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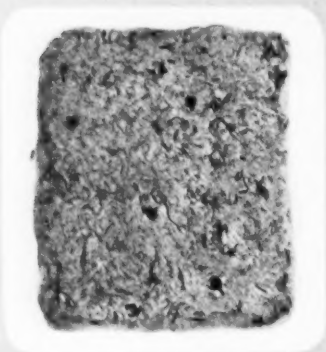

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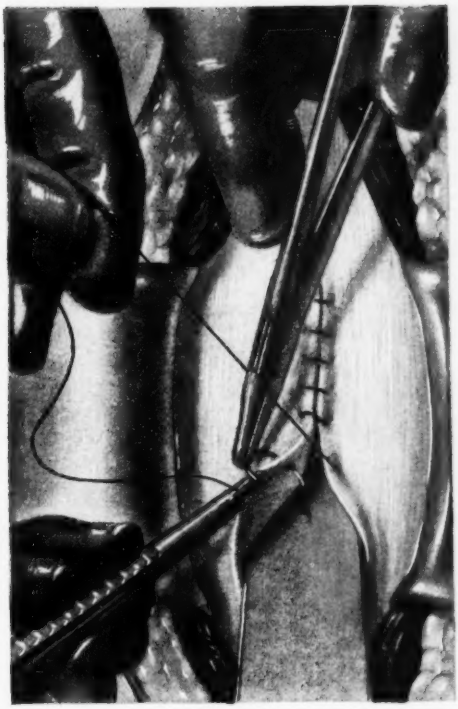

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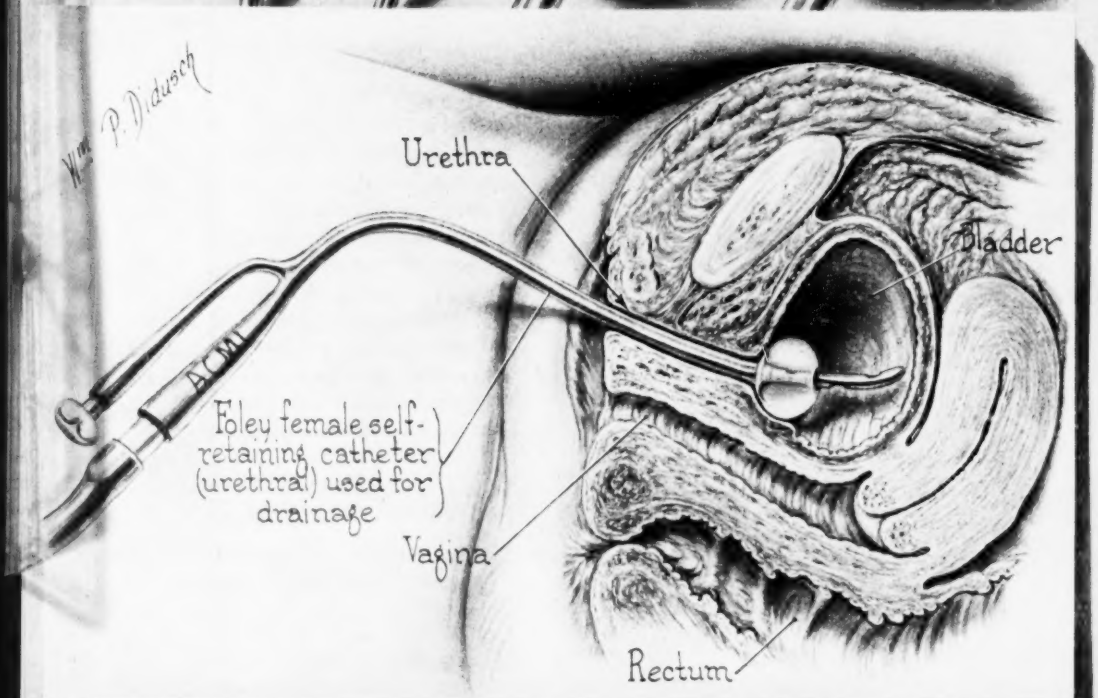

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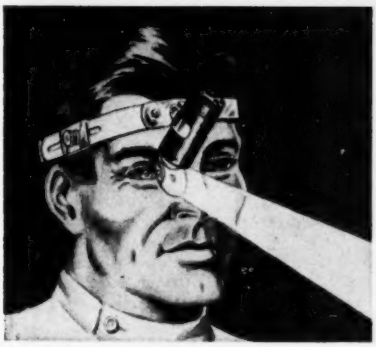

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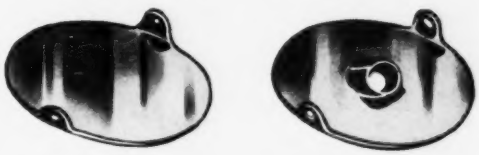

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Editorials

SOME OBSERVATIONS ON THORACIC SURGERY IN GENERAL AND PECTUS EXCAVATUM IN PARTICULAR

THE PAST decade has witnessed rather definite changes in the content of thoracic surgery. An ever-increasing employment of antibiotic drugs in the management of acute respiratory tract infections has decreased sharply the incidence of pneumonia, postpneumonic empyema, and pulmonary abscess, at least as seen in general hospital practice. The latter two diseases at one time furnished a considerable fraction of thoracic surgical case material, especially in the winter months, but are now reduced to a minor role. Despite this and other results of chemotherapy, the field of thoracic surgery continues to expand. Almost every year brings its new surgical procedure or new therapeutic concepts. By way of illustration one has only to recall the enormous progress made in the area of cardiovascular surgery since the first successful ligation of a patent ductus arteriosus was performed in 1938.

One development in thoracic surgery which has contributed in a minor way to over-all progress is the correction of pectus excavatum, or funnel chest. This is not a very rare abnormality if one includes cases of all degrees. It is probably a hereditary defect but is not sex-linked in its transmission. At or soon after birth the patient presents a midline depression of the sternal body. This is quite uniform in its characteristics. The depression begins at, or just below, the manubriogladiolar junction and reaches its maximum depth at the xiphoid level. Indeed, the xiphoid may be so depressed that it approaches the level of the anterior vertebral bodies. The costal cartilages of the third to seventh ribs also take part in the deformity, perhaps secondarily. They are bowed inward to join the depressed sternum, creating the typical funnel defect. The deformity may progress during childhood and adolescence and is usually associated with a significant degree of kyphoscoliosis.

The operative correction of a pectus excavatum deformity is simple in concept. It involves a resection or transection bilaterally of the involved costal cartilages, a lysis and resection of the depressed xiphoid, a transection of the sternum at the manubriogladiolar level, and the elevation of the gladiolus (body of the sternum) to a slightly over-corrected position, which is maintained for a period of about two weeks by wire traction sutures attached to a chest wall splint.

This operation is, of course, a form of thoracoplasty and is not visceral thoracic in nature. It is, nevertheless, a major procedure with a slight mortality risk and a significant complication rate. Possible complications include wound infection, anterior mediastinal sepsis, pneumothorax, empyema, and pulmonary complications.

Therefore the procedure should be advocated only when the deformity is severe or progressive and when its effects constitute a significant threat to the integrity of the individual. Cardiac insufficiency may occur as a complication of pectus excavatum due to displacement of the heart and interference with mediastinal hemodynamics. Kyphoscoliosis of severe grade may demand an attempt at therapeutic control. Disturbances in the psychic sphere are also a consideration. One must weigh these potentialities of the lesion against the morbidity and mortality, however slight, of the corrective procedure. Probably the ideal age group for surgical treatment of pectus excavatum is from 4 to 10 years. Then the technical problems are least, recovery more rapid, and the cosmetic and functional results more satisfactory than when the operation is performed in adults.

GUSTAF E. LINDSKOG, M.D.

DIAGNOSIS AND TREATMENT OF PYLORIC HYPERTROPHY IN THE ADULT

WILLIAM P. KLEITSCH, M.D.
OMAHA

HYPERTROPHY of the pyloric sphincter as a source of symptoms in the adult is an uncommon but by no means rare condition. Recent extensive reviews of the literature have brought the subject up-to-date.[1] Unfortunately, however, in most instances the condition has been described as more or less of a medical curiosity, and diagnosis has been insufficiently stressed. Indeed, Bockus [2] has said, "A positive preoperative diagnosis of pyloric muscle hypertrophy in adults is not possible." It is my opinion, to the contrary, that this condition is associated with sufficient constant roentgenographic features to be diagnosable by the radiologist or the gastroenterologist. An increased awareness of this disease, together with an appreciation of its diagnostic criteria, will bring surgical relief to a number of patients now treated medically for vague abdominal and epigastric symptoms.

In this series of four cases the patient was usually referred to the surgeon as having either stenosing duodenal ulcer or antral carcinoma—diagnoses arrived at jointly by the internist and radiologist and accepted by the surgeon. These diagnostic errors are not necessary, since the roentgenological appearance of pyloric hypertrophy is typical, and in many cases the diagnosis is supported by the history. The adult victim of pyloric hypertrophy is fortunate if the radiologist misdiagnoses his case as carcinoma, for in this instance he will usually come to surgical exploration. If a misdiagnosis of duodenal or antral ulcer is made, the unfortunate victim may be treated medically for a prolonged period with, in view of the pathology, no hope of relief of symptoms. I agree with McClure,[3] who has said: ". . . we urge the greater need of its recognition in every case in which it is present, and its

From the Department of Surgery of the Creighton University School of Medicine and the Surgical Service of the United States Veterans Hospital. This study was initiated at the Lincoln Veterans Hospital, and the case reports are from their files.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. McCann, J. C., and Dean, M. A.: Hypertrophy of Pyloric Muscle in Adult, Surg., Gynec. & Obst. **90**:535-542, 1950. North, J. P., and Johnson, J. H.: Pyloric Hypertrophy in the Adult, Ann. Surg. **131**:316-329, 1950.

2. Bockus, H. L.: Pyloric Muscle Hypertrophy in Adults, in Gastro-Enterology, Vol. I: The Esophagus and Stomach: Examination of the Patient, and Diagnosis and Treatment of Disorders of the Esophagus and Stomach, Including Duodenal Ulcer, Philadelphia, W. B. Saunders Company, 1943, pp. 759-761.

3. McClure, C. C.: Hypertrophy of the Pyloric Muscle in Adults, Surg., Gynec. & Obst. **52**:945-952, 1931.

appropriate treatment by a sufficiently radical operative procedure. Palliation by medical treatment only postpones the day when operation is imperatively required and prolongs the patient's suffering."

Without attempting to become involved in a discussion of the etiology of the condition, I may briefly review several significant observations. It has been well established that congenital pyloric hypertrophy will persist into adult life unless a Rammstedt pyloroplasty is done.[4] It is not difficult to assume that the Rammstedt operation is not done in every case of congenital pyloric hypertrophy. It must follow, therefore, that in cases in which for one reason or another operation is not performed in childhood the anomaly will persist into adult life. This fact suggests why adult pyloric hypertrophy is not as rare a condition as it is generally considered to be—the four cases in this series were discovered in a period of less than five years.

CLINICAL FINDINGS

Pyloric hypertrophy in the adult can produce symptoms as a result of its own pathology or may produce symptoms together with associated or secondary pathology. In uncomplicated cases of adult pyloric hypertrophy the history is typical. It differs most markedly from an ulcer history in that the epigastric pain is aggravated by the ingestion of food and is largely relieved by vomiting. Night pains are notably absent. A relatively high-grade pyloric obstruction may develop, manifested by the development of a postprandial epigastric mass which disappears after vomiting. Physical examination is seldom helpful except in cases in which a dilated stomach is palpable. Palpation of the tumor itself has not been possible in this series and is probably not to be expected.

The most usual complication of adult pyloric hypertrophy is peptic ulceration. The ulceration may occur in either the stomach or the duodenum or within the narrowed, elongated pyloric canal. When the ulceration is in the duodenum, it probably represents a pathological process distinct from and independent of pyloric hypertrophy. It is unlikely that duodenal ulceration and pyloric hypertrophy are etiologically related. On the other hand, peptic ulceration in the stomach above a stenotic and hypertrophied pylorus might well be due to stagnation of the gastric content and elimination of duodenal reflux. This would result in a prolonged exposure of the gastric mucosa to the digestive juices and might play a role in the etiology of such ulcerations. It would seem that prolonged retention of the night secretions of the stomach, in the absence of food, would be most important in this respect. Finally, the ulcers which develop in the stenotic pyloric canal itself are most likely traumatic in origin, secondary to the passage of food through the stenotic pylorus. This hypothesis is supported by the appearance of the ulcer, which is superficial, narrow, and elongated and, on inspection, appears to be an acute traumatic ulcer rather than the typical chronic peptic ulcer.

4. Donovan, E. J.: Congenital Hypertrophic Pyloric Stenosis, Ann. Surg. **124**:708-715, 1946. Fowler, L. H., and Hanson, W. A.: Gastrojejunal Ulcer Following Gastro-Enterostomy Performed 24 Years Before for Pyloric Stenosis of Infancy, Minnesota Med. **23**:602, 1940. Horwitz, A.; Alvarez, W. C., and Ascanio, H.: The Normal Thickness of the Pyloric Muscle and the Influence on It of Ulcer, Gastro-Enterostomy and Carcinoma, Ann. Surg. **89**:521-528, 1929. Wollstein, M.: Healing of Hypertrophic Pyloric Stenosis After Fredet-Rammstedt Operation, Am. J. Dis. Child. **23**:511-517, 1922.

The significance of the history of a patient with pyloric hypertrophy would therefore depend upon the presence of associated peptic ulceration in the upper gastrointestinal tract. In the absence of peptic ulceration the syndrome would be that of simple pyloric obstruction. Pain and vomiting after meals would be prominent, epigastric pain would be precipitated rather than relieved by the ingestion of food, and the symptoms would not respond to the use of antacids. This type of history should lead one to suspect that something other than a peptic ulcer is producing symptoms. In cases of coexistent duodenal or gastric ulceration the clinical history would be indistinguishable from that of a stenosing duodenal ulcer.

ROENTGEN FINDINGS

Roentgenograms of the upper gastrointestinal tract of patients with hypertrophy of the pyloric sphincter are absolutely characteristic. My associates and I have found the roentgen appearance of the lesion to be typical, readily recognizable, and constant. The typical picture is in fact so definite and so constant that it is readily recognizable in roentgenograms published in the studies of other observers on this subject.[3]

The diagnostic picture is that of an elongated and narrowed pyloric canal, the thickened sphincter muscle giving the impression of a filling defect surrounding the pyloric antrum. For want of a better term we have called the characteristic elongation and narrowing of the pyloric canal the "pyloric string sign." This sign is constant and is not obliterated by antispasmodics.

TREATMENT

Since pyloric hypertrophy in the adult represents an organic obstruction to the passage of food through the gastrointestinal tract, it requires, as does congenital pyloric hypertrophy, radical surgical treatment. There is, however, no standard technique to be recommended. Each procedure must be individualized to cope with the pathology discovered by the surgeon at operation. If pyloric hypertrophy is the only pathology discovered, the operation should be the simplest procedure which will adequately relieve the obstruction. Gastroenterostomy is not considered to be adequate treatment, because of the danger of subsequent stoma ulcer. Simple transection of the sphincter, carrying the incision well into the stomach and duodenum, with transverse closure of the resulting defect (the Heineke-Mikulicz pyloroplasty) has the advantage of simplicity and the least derangement of the normal physiology (Fig. 1*A*). If feasible, it is the preferred procedure. In some patients the muscular hypertrophy may have developed to a point where transverse closure of a transection might be awkward because of difficulty in inverting the thickened muscle. In this type of condition we suggest the Billroth I type of operation or some modification of it; in effect, excising the sphincter muscle completely and then restoring the normal continuity of the gastrointestinal tract (Fig. 1*B*).

If peptic ulceration is present, a more radical operation will be needed to give the patient relief of symptoms and adequate treatment. If a duodenal ulcer is present or evidence of duodenal fibrosis or stenosis can be demonstrated, an ulcer operation should be done. This will require a high, subtotal gastrectomy (Fig. 2*A*). If the ulceration is gastric, a subtotal gastrectomy is again indicated; however,

because of the danger of cancer, which is difficult to exclude by examination, the resection should be done at a safe distance above the ulcer and the regional lymph nodes should be included in an en bloc type of resection (Fig. 2*B*).

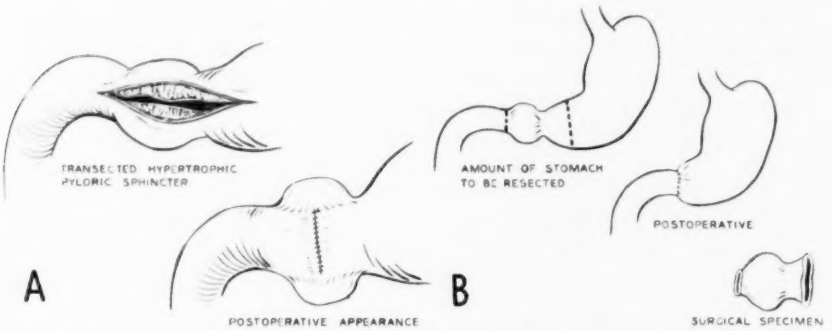

Fig. 1.—*A*, diagrammatic representation of the Heineke-Mikulicz type of pyloroplasty for the relief of obstruction due to pyloric hypertrophy. *B*, diagrammatic representation of pyloric resection with subsequent repair by means of a Billroth I type of procedure.

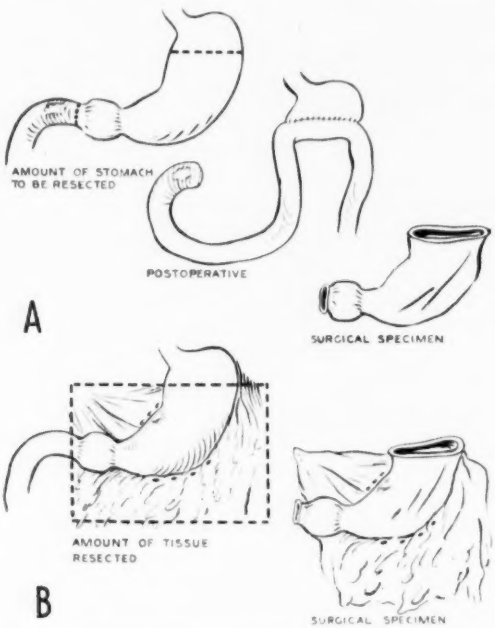

Fig. 2.—*A*, diagram illustrating the operative treatment of pyloric hypertrophy when associated with a duodenal ulcer. *B*, diagram suggesting the operative procedure to be employed when a gastric ulcer is found complicating pyloric hypertrophy.

REPORT OF CASES

CASE 1.—E. F. A., a 50-year-old white man, was admitted to the hospital on March 21, 1949, for treatment of bilateral inguinal hernias. Physical examination revealed nothing abnormal except some tenderness in the epigastrium and bilateral, reducible, inguinal hernias. Because

of the epigastric tenderness and some vague abdominal complaints elicited on systemic survey, a gastrointestinal study was done. The roentgen diagnosis was neoplastic involvement of the pylorus and gastric antrum with associated constriction and retention of a fourth of the meal at three hours (Fig. 3). Despite the fact that this patient did not appear clinically to have carcinoma of the stomach, he was considered a subject for surgical exploration because of the roentgen diagnosis. He was operated upon on April 12, and a pronounced hypertrophy of the pyloric muscle was discovered. There were many lymph nodes in both the lesser and the greater

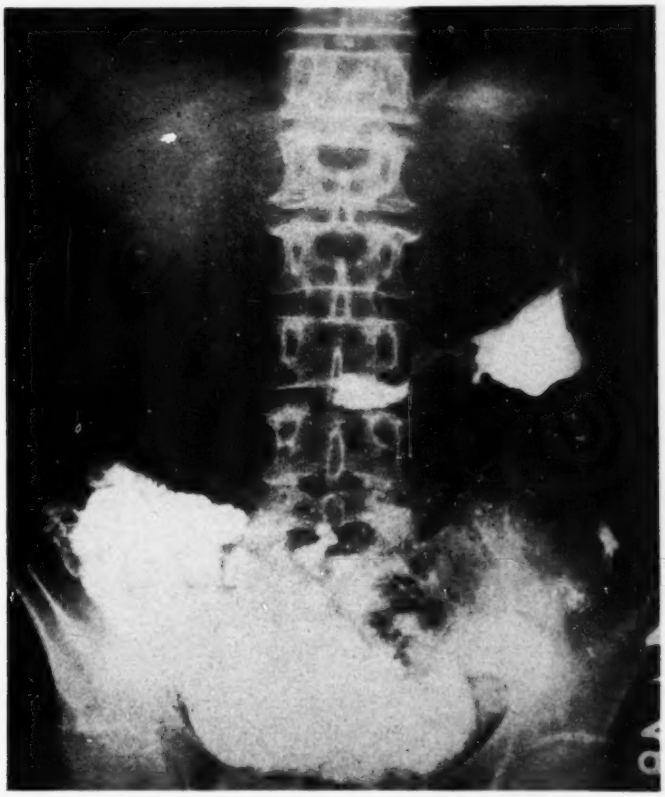

Fig. 3.—Roentgenogram of the upper gastrointestinal tract in Case 1, showing the amount of three-hour retention. The arrow indicates the well-outlined "pyloric string sign."

curvature. Because of the possibility of malignancy, a "cancer type" of subtotal gastrectomy was done; a retrocolic isoperistaltic Polya technique was used, and the hypertrophied omental lymph nodes were resected en bloc with the stomach (Fig. 4 *A*). Study of the resected portion of stomach revealed a firm and hypertrophic pyloric ring; 8 cm. above the pylorus, on the lesser curvature of the stomach, was a peptic ulcer 1 cm. in diameter which, apparently, was the reason for the omental lymphadenopathy (Fig. 4 *B*). The pathological diagnoses were (1) hypertrophy and fibrosis of the muscularis of the pylorus and (*2*) gastric ulcer on the lesser curvature of the stomach. The patient made an uneventful recovery from the operation and was discharged on the eighth postoperative day.

Case 2.—W. H. B., a 58-year-old white man, was admitted to the hospital on Jan. 6, 1950, for treatment of a chronic duodenal ulcer combined with a gastric ulcer. He gave a history of epigastric distress of at least 25 years' duration. He had been treated one month previously for combined duodenal and gastric ulcer. Physical examination gave essentially negative results

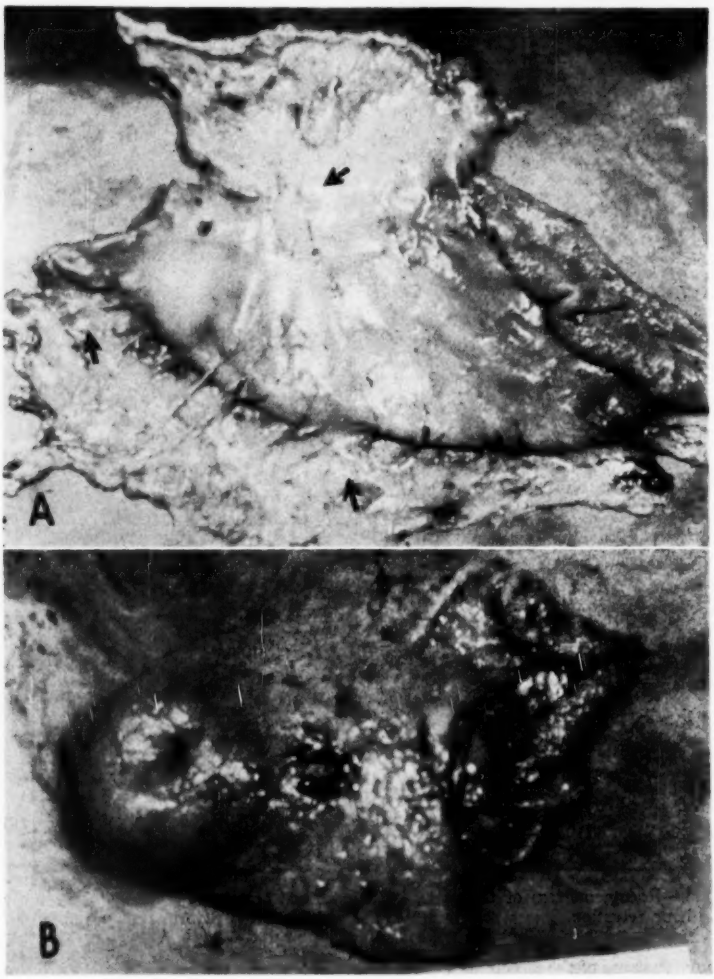

Fig. 4.—*A*, the surgical specimen of the lesion which produced the roentgenographic appearance in Figure 3 (Case 1). Note the pronounced pyloric hypertrophy and the omental lymph nodes indicated by arrows. *B*, the surgical specimen inverted to show the thickened pyloric muscle and stenotic canal, resembling the human cervix in both shape and size. The ulcer on the lesser curvature is benign and apparently the reason for the hyperplastic mesenteric and omental lymphadenitis.

except that the distended stomach was palpable. Gastrointestinal roentgenograms revealed what was interpreted to be a persistent pylorospasm as well as a gastric ulcer and a duodenal ulcer (Fig. 5).

The patient was prepared for an operation and subjected to laparotomy on Feb. 3. At operation a calculus was found in the gall bladder and the pylorus was found to be markedly hypertrophied. There was evidence of a recently healed gastric ulcer, but the duodenum was perfectly normal. An appendectomy and cholecystectomy were done in the usual manner, and a Heineke-Mikulicz type of pyloroplasty was performed to relieve the pyloric obstruction. The patient made an uneventful recovery from the operation and was discharged on the 10th post-operative day. A month later he was completely asymptomatic.

Fig. 5.—Roentgenogram of the upper gastrointestinal tract in Case 2, showing the narrow and elongated pyloric canal.

Case 3.—J. S., a 56-year-old white man was admitted to the hospital on March 8, 1950, for treatment of a duodenal ulcer or malignant tumor. He complained of epigastric pain of four months' duration which came on after eating and was partially relieved by vomiting. However, he also noted cramp-like pain in the epigastrium when the stomach was empty. Three months prior to admission he consulted his private physician, who diagnosed a peptic ulcer and treated him by diet, but with no improvement. He had had a similar episode 25 years earlier, at which time he was also treated for peptic ulcer.

Physical examination showed nothing abnormal except tenderness in the epigastrium. Laboratory studies revealed no pathology. Roentgenograms of the chest showed inactive residuals of tuberculosis. Gastrointestinal roentgenograms revealed a narrow, channel-like passage existing between the antrum and the duodenum (Fig. 6). The impression obtained by the radiologist was of an inflammatory lesion in the prepyloric region and possibly in the pylorus.

Fig. 6.—Roentgenogram of the upper gastrointestinal tract in Case 3, again showing the typical pyloric string sign.

The patient was prepared for operation, and a laparotomy was done on March 22. A hypertrophied pyloric muscle was discovered, and it was treated with a Billroth I type of gastric resection. Histopathological study of the resected portion of stomach revealed muscle hypertrophy and inflammatory edema of the pylorus (Fig. 7). A mucosal ulcer 4 mm. in its greatest diameter was found on the posterior wall of the pyloric canal. Recovery from the operation was uneventful, and the patient was discharged on the 12th postoperative day.

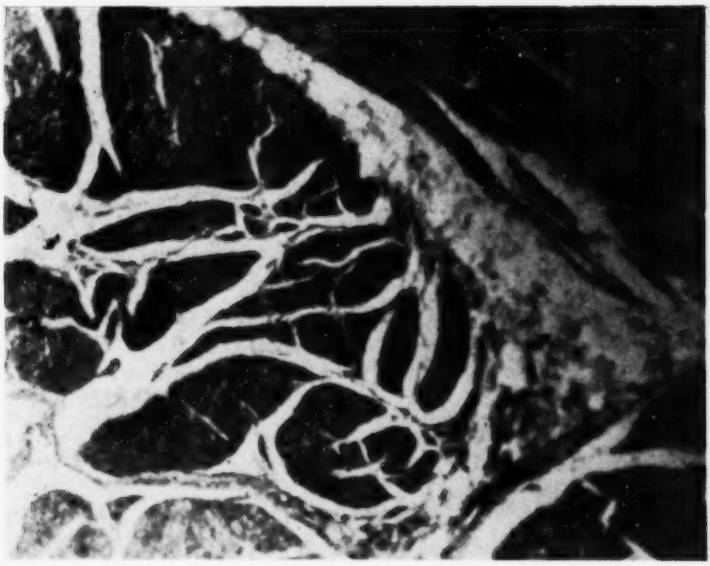

Fig. 7.—Low-power photomicrograph of a histological section taken from the surgical specimen removed in Case 3. Note the hypertrophied muscle bundles characteristically separated by areas of edema.

Fig. 8.—Roentgenographic findings in Case 4, showing the typical pyloric string sign. This is the one case of this series which was diagnosed preoperatively—on the basis of these findings.

CASE 4.—H. H. B., a 38-year-old white man was admitted Sept. 22, 1950, for the treatment of a peptic ulcer. He had been treated for "stomach trouble" with diet and medication for about five years. In the morning two days before admission he became ill while at work and passed a large, black, tarry stool. Although he felt weak, he continued to work that day, but that evening he again passed a large, tarry stool, after which he lost consciousness for a few minutes. He then applied for hospitalization. On admission to the hospital he had 3,910,000 red cells and 11.8 gm. of hemoglobin, and by the next day his blood count had fallen to 3,300,000 red cells and 11 gm. of hemoglobin. He was treated with blood transfusions until his red cell count was restored to 4,720,000, with 15.1 gm. of hemoglobin. The diagnosis based on gastrointestinal roentgenograms was ulceration which appeared to be in the pyloric channel itself, with marked spasm, stenosis, and narrowing of the pylorus (Fig. 8).

The patient was prepared for operation and on Oct. 25 a laparotomy was done. Pyloric hypertrophy was demonstrated, as well as evidence of fibrosis and inflammation in the first portion of the duodenum and in the pyloric area. Because of the definite evidence of a bleeding peptic ulcer, a subtotal gastrectomy was felt to be the procedure of choice, and a posterior, antiperistaltic Polya gastrectomy was accomplished. The postoperative course was uneventful.

COMMENT

Hypertrophy of the pylorus in the adult as a cause of symptoms occurs more frequently than is generally appreciated. Even in the best clinics the condition is usually unrecognized and not diagnosed unless an operation is performed. It is unfortunate that the operations, when they occur, are the result of a misdiagnosis. Since this is a benign condition and the surgical relief obtained is complete and permanent, a more strenuous effort to make a diagnosis of hypertrophy of the pylorus in the adult is indicated. The roentgenographic findings are so consistent that, in retrospect, I feel it possible to say without hesitation that the condition should have been diagnosed preoperatively in each of the four cases herein reported. In reproductions of roentgenograms published in other papers on the subject,[8] the same characteristic picture is discovered, a fact which supports the contention that this condition should be diagnosed before operation. Correct diagnosis and surgical treatment offer hope for the complete amelioration of symptoms in patients otherwise doomed to chronic invalidism.

SUMMARY

1. The peroperative diagnosis of pyloric hypertrophy in the adult is not made as frequently as is possible.

2. The "pyloric string sign" is identified as a characteristic roentgen finding.

3. Individualization of operative procedures to include treatment of associated pathology is recommended. The operative procedures suggested are the Heineke-Mikulicz pyloroplasty or the Billroth I partial gastrectomy for simple, uncomplicated pyloric hypertrophy. If a duodenal ulcer coexists, an ulcer type of gastrectomy is indicated, whereas a coexistent gastric ulcer would require an en bloc type of resection.

CATASTROPHIC COMPLICATIONS OF HIATUS HERNIA

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OMAHA

AN ESOPHAGEAL hiatus hernia is frequently asymptomatic or unsuspected until it is discovered accidentally when roentgenograms of the gastrointestinal tract are made because of other pathology.[1] Not uncommonly, however, such hernias do produce symptoms. It is important to note that these symptoms, although mild and intermittent, form a definite symptom complex if truly caused by hiatus hernia. This symptom complex consists of substernal or epigastric pain, acid eructations, and, most characteristically, aggravation of the pain precipitated by maneuvers which increase intra-abdominal pressure.[2]

Because of the fact that many esophageal hiatus hernias are asymptomatic and many of those that are symptomatic are only mildly so, there has been a controversy as to what should be done about them. Errors in diagnosis are frequent, and the significance of hiatus hernia is often overlooked. Frequently the dilemma is solved (?) by the physician by prescribing medical treatment consisting of a bland diet, administration of antacids and antispasmodics, and various postural exercises.[3] Most patients can exist indefinitely on a medical regimen if the physician and patient are satisfied with a chronic state of semi-invalidism.[4] It must be agreed, however, that as far as treatment of the hernia is concerned medical management must be considered to be procrastination. It cannot be argued that medical management has any influence on the anatomical defect which is present.[5] For specific, etiological treatment of the condition a surgical operation is necessary.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Bowden, L., and Miller, C. J.: Massive Hematemesis from Hiatus Hernia: Report of 4 Cases with Discussion of Etiology, A. M. A. Arch. Surg. **63**:143-146 (Aug.) 1951. (*b*) Brick, I. B., and Amory, H. I.: Incidence of Hiatus Hernia in Patients Without Symptoms, Arch. Surg. **60**:1045-1050 (June) 1950.

2. (*a*) Richards, G. G., and Crockett, K. A.: Hiatus Hernia, Arch. Surg. **58**:411-418 (April) 1949. (*b*) Rossien, A. X.; Reuling, J. R., and Stanton, A.: A Study of Hiatus Hernia, Am. J. Digest. Dis. **17**:69-76 (March) 1950. (*c*) Simmons, E. E.; Long, R. S.; Hunt, H. B., and Moore, R. C.: Hiatus Hernia: Analysis of 25 Cases, Arch. Int. Med. **86**:253-265 (Aug.) 1950.

3. (*a*) Pickhardt, O. C.; Rafsky, H. A., and Ghiselin, F. H.: Treatment of Hiatus Hernia in Older Persons, J. A. M. A. **142**:310-315 (Feb. 4) 1950. (*b*) Rossien, Reuling, and Stanton.[2b] (*c*) Simmons, Long, and Hunt.[2c]

4. Clerf, L. H.; Shallow, T. A.; Putney, F. J., and Fry, K. E.: Esophageal Hiatal Hernia, J. A. M. A. **143**:169-172 (May 13) 1950.

5. Surgical Forum: Esophageal Hiatus Hernia, Arch. Surg. **60**:633-634 (March) 1950.

These points are important to consider, since, in addition to the two types of hiatus hernia mentioned, the asymptomatic and the mildly symptomatic, there is a third type, in which the hiatus hernia is either associated with or productive of pathology which may be fatal. It is important, therefore, before embarking on a long-continued course of medical therapy to be positively reassured that the hiatus hernia being treated is not one which may develop a catastrophic complication.

INDICATIONS FOR SURGICAL TREATMENT

Pain, aggravated by maneuvers which increase intra-abdominal pressure, such as bending, stooping, lifting, and straining, is frequently severe enough to be disabling and should always be considered an indication for some type of surgical procedure. One of the commonest findings in hiatus hernia is chronic, mild, gastrointestinal hemorrhage.[6] The first sign of this chronic bleeding may be the development of an apparently causeless secondary anemia, the hernia being discovered only after careful examination of the gastrointestinal tract. Gastrointestinal hemorrhage associated with an esophageal hiatus hernia is due to peptic ulceration either in the herniated portion of the stomach or in the lower esophagus.[1a] It must, therefore, be considered to be as ominous a symptom as bleeding from a peptic ulceration elsewhere in the gastrointestinal tract. Especially in patients over 40, severe or repeated gastrointestinal hemorrhage due to an esophageal hiatus hernia should be considered a positive indication for surgical treatment. The indications for the surgical treatment of an esophageal hiatus hernia can be summarized in the statement that any such herniation which produces any symptoms definitely attributable to it should be treated by operation.

TREATMENT

There are two surgical procedures available for the treatment of esophageal hiatus hernia. The procedure of choice is an esophageal hiatus hernioplasty by either the thoracic [7] or the abdominal route. In addition there is an operation which might be termed a procedure of necessity and consists of left phrenicoexeresis.[3a] The selection of the abdominal or thoracic route for hiatus hernioplasty depends upon the individual case and to some extent upon the preference of the surgeon. The abdominal approach is technically more difficult, but it permits a more complete exploration of the abdominal viscera and may be preferable, especially in cases in which associated intra-abdominal pathology is suspected. The transthoracic approach is technically easier and is particularly well suited to those cases in which exploration of the esophagus is more important than exploration of the abdominal viscera. Repair of the hernia can be accomplished with equal effectiveness through either approach.

Phrenicoexeresis for hiatus hernia is not the ideal treatment, since it does not repair the basic anatomical defect. Frequently it produces unpleasant sequelae due to paralysis of the diaphragm, most prominent of which are postprandial distention, gastric retention, and difficulty in expelling swallowed air. Furthermore, the procedure is still so new that a careful analysis of the long-term results in patients who

6. Simmons, Long, and Hunt.[2c] Surgical Forum.[5]

7. Sweet, R. H.: Esophageal Hiatus Hernia of the Diaphragm: The Anatomical Characteristics, Technic of Repair, and Results of Treatment in 111 Consecutive Cases, Ann. Surg. **135**: 1-13 (Jan.) 1952.

have had this operation will be necessary before a final evaluation of the method can be made. However, as a temporizing measure it offers the possibility of relief, if not cure, to patients who, for one reason or another, are not suitable for hiatus hernioplasty. The philosophy behind this approach to the problem is that paralysis will result in muscular atrophy of the diaphragm, which will eliminate the constricting muscular ring thought to produce the unpleasant symptoms.[18] The procedure has the added advantage that if it is unsuccessful it will not prohibit doing the operative procedure of choice at a later date. In my opinion it is the least that can be done in the way of treatment for a symptomatic hiatus hernia, and when this method is used it should always be combined with conscientious and prolonged medical management and observation.

REPORT OF CASES

The following case reports are included as examples of serious complications associated with or produced by inadequately treated or untreated esophageal hiatus hernias.

CASE 1.—J. W. H., a 60-year-old white man was admitted to the hospital on Nov. 10, 1949, for the treatment of a bleeding peptic ulcer. He had awakened from sleep six hours prior to admission feeling sweaty and weak and had vomited a large amount of coffee-ground material. He gave a history of having had stomach trouble "for about 35 years" and had had an episode of painless hematemesis eight months earlier.

On physical examination the evidence of blood loss was only moderate, and no transfusions were given. He responded to ulcer management, and, although roentgenographic studies revealed the presence of a large esophageal hiatus hernia, it was decided that in view of his age, arteriosclerotic heart disease, and the chronic nature of his condition, operation was best deferred. He was discharged Dec. 16 on a weight-reduction diet with instructions to return if any more bleeding occurred.

Three days later (Dec. 19) he returned to the hospital bleeding profusely through the nose and mouth. He had bled four times in the three days since his discharge from the hospital and was in shock, with a blood pressure of 96/70. He was given plasma and whole blood, with oral, topical administration of thrombin, but the bleeding continued. An emergency operation was decided on, as urgently needed to stop the massive hemorrhage.

At operation (Dec. 19) no sign of a duodenal ulcer could be discovered. A gastrotomy was made, and the mucosa of the fundus of the stomach was found to be irregularly ulcerated and bleeding. The gastrotomy was closed; an abdominal vagotomy and a splenectomy were performed, followed by mobilization of the greater curvature of the fundus of the stomach, care being taken completely to devascularize this area. The esophageal hiatus hernia was repaired, a gastrojejunostomy was made, and the procedure terminated. A total of 4,000 cc. of blood was given during the operation, in addition to 4,000 cc. given prior to the operation. The patient was returned to the ward in fairly good condition, although he continued to vomit bright red blood immediately after the operation. The bleeding was controlled within 12 hours, and he began to convalesce slowly.

On the seventh postoperative day (Dec. 26) a deep wound separation was suspected. This became obvious two days later and required closure with sutures. In the postoperative period he repeatedly passed tarry stools, which suggested that the bleeding was not completely controlled, and blood transfusions were given daily. He did fairly well after resuture of the wound until Dec. 30, when a mild icterus developed which could not be adequately explained, although a hepatocellular type of jaundice was suspected. Nevertheless, he continued to improve in spite of a mild fever and by Jan. 3, 1950, seemed to be out of danger and on his way to recovery. He was able to be out of bed and had no complaints. In the evening of Jan. 3, he suddenly became confused and dyspneic, and a hypotension of 90/60 developed. He was placed in an oxygen tent but responded poorly to supportive measures. A diagnosis of pulmo-

nary embolism was made. His condition gradually deteriorated, and signs of a hydrothorax developed. A thoracentesis was done, and 600 cc. of clear, straw-colored fluid was removed from the right thorax without relief. In spite of all efforts his condition continued to deteriorate, and he died Jan. 8, 1950.

At autopsy it was discovered that death was due to multiple, acute, pulmonary emboli in the right lung. The cardiac end of the stomach (which had been in the hernia) and the lower end of the esophagus were denuded of epithelium in irregular patches. A small amount of pancreatic necrosis was present, which apparently accounted for the jaundice.

The unfortunate outcome in this instance might well be attributed to poor judgment. The patient was known to have bled repeatedly from the gastrointestinal tract, and he was known to have a large hiatus hernia. In the face of this knowledge he was not operated on because he was too old and too arteriosclerotic. This was an error, since it is generally accepted that advanced age and arteriosclerosis are probably the two most urgent indications for operative treatment of gastrointestinal bleeding. Since hindsight always appears more cogent than foresight, one must admit that hiatus hernioplasty might not have prevented the fatal, massive hemorrhage, but one is forced to assume that it might have done so, since the bleeding was controlled by the operation and death was caused not by exsanguination but by late, pulmonary emboli. A prophylactic hiatus hernioplasty could certainly be better expected to succeed than one done under these trying circumstances.

CASE 2.—L. M. B., a 52-year-old white man, was admitted to the hospital on Nov. 8, 1950, for emergency treatment of coronary thrombosis. He had been hospitalized in 1944 for the treatment of duodenal ulcer and since that time had felt fairly well, having been able to maintain constant employment. During the summer of 1950 he had occasional attacks of "heartburn," which were relieved by soda.

One week prior to the present admission the heartburn became more severe, causing him to awaken. He was seen by a physician, and an ulcer diet and aluminum hydroxide gel (amphojel®) were prescribed. The distress gradually progressed to a severe cramping pain which was most acutely felt in the right lower abdomen. It increased in severity over a period of several hours, finally becoming most severe in the epigastrium and radiating to the precordium and into the left shoulder and arm. A physician was called shortly after the onset of the pains, and he found the patient to be extremely dyspneic and in shock. A sedative was administered, and the patient was sent to the hospital the next afternoon as a cardiac problem.

At physical examination the temperature was 104 F., pulse rate 140, respirations 32, and blood pressure 90/60. The patient was well-nourished, acutely ill, and dyspneic. Cyanosis was noted in the lips and finger tips, and there was some evidence of dehydration. Both sides of the diaphragm were elevated, and occasional rhonchi were heard in the right thorax. A loud friction rub was heard over the left chest laterally and posteriorly and obscured all breath sounds. The heart appeared to be normal in size, and its sounds were of normal quality, rate, and rhythm; no murmurs were heard. The abdomen was diffusely tender to palpation but was soft, and no definite muscle guarding could be demonstrated. There was questionable, unlocalized, rebound tenderness. Percussion of the abdomen revealed anterior tympany with dullness in the flanks, and auscultation showed a complete absence of bowel sounds. Leucocytosis with a count of 10,400 and 74% polymorphonuclear neutrophiles was found, and the serum amylase was 185 mg. per 100 cc.

A flat plate of the abdomen made at this time revealed a single loop of gas-filled intestine in the left upper quadrant. Free air beneath the diaphragm could not be demonstrated. A roentgenogram of the chest was unsatisfactory but suggested elevation of the diaphragm and indefinite mottling in the left lower lobe. An electrocardiogram showed an inverted T wave in Lead III, which was not significant as the tracing was otherwise unchanged from his previous record. On the basis of these findings a diagnosis of early, fulminating, left lower lobe pneumonia or possibly a pulmonary embolus was made, the abdominal manifestations being attributed to a secondary paralytic ileus.

The patient was treated for pneumonia, with some improvement in his symptoms. On Nov. 10, two days after admission, his temperature had fallen to 100.6 F., but the white count had risen to 15,600, with 91% polymorphonuclear neutrophiles. A roentgenogram of the chest at this time did not support the diagnosis of pneumonia, and other films of the abdomen now revealed the presence of free air. A small gas shadow which was visualized behind the heart, extending above the level of the diaphragm, could not be adequately explained. A diagnosis of perforated hollow viscus was made, and in the evening of Nov. 10 a laparotomy was performed. This revealed a generalized peritonitis. There was some difficulty in establishing the reason for the peritonitis until the stomach was pulled down into the wound. This maneuver revealed a moderately large esophageal hiatus hernia. The fundus of the stomach had been inside the hernia sac, and a perforated gastric ulcer was discovered in the anterior wall of the stomach just below the esophagus, in that portion of stomach which lay within the hiatus hernia. The ulcer lay just above the level of the diaphragm at the point of maximum diaphragmatic constriction. The perforation was closed with several interrupted catgut sutures, and the defect was covered with omentum. The postoperative condition became increasingly critical, and the patient died on the evening of Nov. 11.

Postmortem examination revealed a left subphrenic abscess, a generalized peritonitis, a hiatus hernia, and a recently sutured, perforated, gastric ulcer.

The unfortunate outcome in this case was due to the fact that the man entered the hospital not only in an acute emergency state but also as a diagnostic problem. It is understandable that the perforation of a peptic ulcer of the stomach into a hiatus hernia sac would produce symptoms more likely to be taken for those of coronary heart disease than an abdominal condition. Confusion of hiatus hernia symptoms with cardiac symptoms is not uncommon,[8] although perforation of an ulcer in the hernia is rare.[1a] The perforation did, in fact, occur intrathoracically rather than intra-abdominally, and it progressed to an abdominal condition only because the herniated viscus was separated from the other intrathoracic viscera by the hernia sac.

It is interesting to speculate as to the treatment for duodenal ulcer which the patient had received six years prior to his final illness. No evidence of duodenal ulceration was discovered at autopsy, and one is probably justified in assuming that the symptoms earlier attributed to a duodenal ulcer were, in fact, produced by an undiagnosed hiatus hernia and gastric ulcer.

CASE 3.—H. E. H., a 57-year-old white man, entered the hospital on May 26, 1950, complaining of inability to swallow of 18 hours' duration.

During the past two years the patient had suffered recurrent acid eructations associated with upper abdominal distention following meals. The distention was relieved by eructation and vomiting. This postprandial distress was a daily occurrence but had not interfered with his appetite, and there had been no weight loss. On four or five occasions he experienced a sharp, high, epigastric pain which caused a shortness of breath and prevented him from either swallowing or vomiting. These episodes, however, were evanescent, and after 5 or 10 minutes the pressure would ease and the pain disappear and he would feel normal again. These episodes were always relieved spontaneously, without treatment. In the evening of the day prior to admission he had a sudden, choking sensation while eating his evening meal and was forced to stop. The following morning he was unable to eat, each attempt at swallowing resulting in a feeling of smothering, which was relieved only by regurgitation. He felt as though the esophagus was obstructed at the end of his sternum. He was admitted at 4 p. m. the next day because of a persistence of symptoms. There was no history of hematemesis or tarry stools.

8. Clerf, Shallow, Putney, and Fry.[4] Richards and Crockett.[2a]

At physical examination the patient was seen to be tall, thin, somewhat undernourished, and in acute distress. A careful physical examination gave completely negative results, as did the laboratory examinations.

Immediately after admission to the hospital roentgen studies demonstrated a complete obstruction of the esophagus just above the diaphragm. The roentgenograms revealed a peculiar shadow with a convex edge completely obstructing the lower end of the esophagus. The possibility of a tumor was considered, but the roentgenologist was disinclined to commit himself to such a diagnosis. An esophagoscopic examination, done immediately after the roentgenological studies, revealed no pathology, and the esophagoscope could be passed into the stomach with ease. After these maneuvers, a Levine tube was passed into the stomach through a nostril, and the patient was considered to be no longer in a state of emergency.

On June 5 an exploratory laparotomy was done and an esophageal hiatus hernia was discovered. The omentum had become incarcerated within the hernia sac, from which it could be removed only by moderate traction. The end in the hernia was about the size of a hen's egg, thickened, and undoubtedly the cause of the esophageal obstruction. The offending piece of omentum was amputated, and the defect in the diaphragm was closed with interrupted cotton sutures.

This case should be considered to be a medical rarity, since incarceration of omentum in a hiatus hernia is a most unusual finding. The dramatic symptoms of esophageal obstruction made surgical exploration mandatory, and since the difficulty was unusual rather than serious, a completely satisfactory result was achieved.

Case 4.—R. S., a 58-year-old white man, was admitted to the hospital on July 14, 1948, complaining of persistent vomiting and epigastric pain. He stated that he had been having considerable nausea and vomiting unrelated to meals, that he was weak and nervous and had trembling of the arms and hands. The admitting physician thought the symptoms had a strong functional element.

Physical examination revealed that the patient, who was ambulant, was well developed and well nourished. He showed signs of acute anxiety but was in no evident physical distress. A well-healed scar in his right thigh—the result of an old war wound—and a small lymph node in the left supraclavicular fossa were the only abnormal findings recorded. Roentgenograms of the upper gastrointestinal tract revealed what was interpreted to be a polypoid growth in the lower end of the esophagus. This was confirmed by subsequent esophagograms, which also disclosed an esophageal hiatus hernia. Esophagoscopy was done on three occasions and revealed no pathology, although a biopsy specimen taken on one occasion showed ulceration of the mucosa. A Minnesota multiphasic personality inventory and psychiatric consultation disclosed the patient to be a hypochondriac with depressive and hysterical tendencies. A biopsy specimen of the left supraclavicular lymph node was reported as showing chronic, nonspecific lymphadenitis.

Surgical exploration was long deferred because the patient's complaints were apparently largely psychoneurotic in origin, but, because of the persistence of the complaints and the positive roentgenographic findings, a transthoracic exploration of the esophagus was finally done on Dec. 16. An esophageal hiatus hernia about the size of a golf ball was immediately discovered. Above the herniation there was an area of induration of the wall of the esophagus involving approximately 10 cm. of the distal end of the organ. With the induration there was what was interpreted to be an inflammatory reaction, which bound the esophagus to the adjacent mediastinal structures to such an extent that mobilization of it was felt to be unsafe. A large lymph node in the mediastinum was removed for histopathological examination, and, since the esophageal reaction was felt to be inflammatory, the entire syndrome was thought to be explainable on the basis of a peptic ulcer in the lower esophagus, with inflammatory contracture producing a shortening and a secondary hiatus hernia. A bilateral vagotomy was done, but the hiatus hernia was not repaired because the esophagus was too short and could not be adequately mobilized.

The postoperative course was prolonged owing to a series of unfortunate complications starting with the development of atelectasis and pneumonitis on the second postoperative day.

Six days after the operation (Dec. 22.) signs of a deep thrombosis in the right calf were noted, and shortly thereafter the symptoms of a pulmonary infarct became obvious. This impression was supported by a roentgenogram of the chest, and treatment with anticoagulants and antibiotics was instituted. In spite of all these complications the patient made a complete recovery and became ambulant.

Much to everyone's surprise the histopathological report on the mediastinal lymph node removed at the operation was lymphosarcoma. The diagnosis of peptic ulceration was, therefore, abandoned, and on Jan. 3, 1949, deep roentgen therapy directed to the mediastinum was started. A total of 5,700 r was given, and a cancerocidal dose was felt to have been administered. About two weeks later (Jan. 20) the patient became rather ill, with dyspnea, cyanosis, a small rapid pulse, and a low blood pressure. These findings were interpreted to represent a posterior mediastinitis, a result of the deep roentgen therapy, producing an edematous constriction of the inferior vena cava. The patient recovered from this incident with symptomatic management and was discharged, ambulant, on Feb. 11. He was rehospitalized in April, 1951, for a transurethral resection of the prostate, at which time no evidence of recurrence of the mediastinal lymphosarcoma was noted.

Surgical exploration in this case was long delayed because of difficulty in evaluating the symptoms. The hiatus hernia was not the primary disease but was probably a result of the shortening of the esophagus due to involvement in the mediastinal lymphosarcoma. However, the establishment of the correct diagnosis by surgical exploration and biopsy, followed by specific treatment, resulted in a satisfactory control of the lymphosarcoma, which after three years had shown no further evidence of extension.

CASE 5.—C. E. M., a 60-year-old white man, was admitted to the hospital for the treatment of severe anemia, diverticulosis of the colon, and cirrhosis of the liver. He complained of weakness and dyspnea of six months' duration and an episode of hematemesis three months prior to admission. He had had no further hematemesis, but his stools had been black on several occasions.

Physical examination gave results within normal limits except for some pallor of the mucous membranes. A blood count revealed 3,760,000 red cells and 10.5 gm. of hemoglobin; the hematocrit reading was 39%. Roentgenograms of the gastrointestinal tract were reported as showing (1) esophageal hiatus hernia and (2) diverticula of the second portion of the duodenum. A further note was made: "There is a slight eccentricity of the pyloric canal. This is probably not of significance." The patient was treated with a Sippy regimen, blood transfusions, and iron therapy. The blood picture improved, although the stools continued to show occult blood during his period of hospitalization. He was discharged on Sept. 21, 1951.

The patient was seen in December and again in January, at which time he again showed clinical evidence of hemorrhage. He was readmitted to the hospital on Jan. 22, 1952. At this admission he stated that he had been asymptomatic for only a month after his previous hospitalization and thereafter had noted frequent burning epigastric pain not related to meals or food. He had also noticed a loss in weight.

Results of physical examination were unremarkable. The blood count again revealed anemia with 3,300,000 red cells and 8 gm. of hemoglobin. Roentgenograms of the gastrointestinal tract disclosed definite narrowing of the distal third of the stomach, which was diagnosed as an organic lesion, probably malignant.

The patient was subjected to laparotomy on Feb. 29. A huge tumor of the antral portion of the stomach, approximately 8 cm. in diameter, was discovered. The lesion was freely movable and was resected, although metastasis to the omental nodes had occurred.

Carcinoma of the stomach is not a complication of hiatus hernia. However, repeated gastric hemorrhage in an elderly man is strong indication for laparotomy, regardless of its origin. In this instance erroneous interpretation of the significance of a hiatus hernia resulted in a four months' delay in surgical exploration.

COMMENT

The most important symptoms of esophageal hiatus hernia are (1) epigastric pain influenced by changes in intra-abdominal pressure and (2) gastrointestinal hemorrhage. These symptoms are due to incarceration or strangulation and peptic ulceration, respectively.

It seems difficult to justfy a point of view which does not accept an operation as the proper treatment for any hernia which causes symptoms of strangulation or incarceration. The bleeding accompanying a hiatus hernia is accepted as being due to peptic ulceration of the lower esophagus or upper stomach. Thus this ulceration is one of the few examples of peptic ulceration in man for which a specific cause is demonstrable. Surgical repair of the hernia offers specific treatment of the condition, as contrasted with the nonspecific regimen of diet and antacids.

The serious nature of symptomatic hiatus hernia is not emphasized by most published statistics. Most of these studies have been reported by internists, who naturally see the condition in its mildly symptomatic or asymptomatic form. The catastrophies, when they occur, force surgical intervention, and the case reports are then filed among surgical records by the name of the complication. The hiatus hernia becomes all but forgotten in the face of the more obvious pathology. The cases herein reported might have been cataloged as (1) pulmonary embolism secondary to operation for gastrointestinal hemorrhage due to peptic ulceration, (2) generalized peritonitis due to perforated gastric ulcer, (4) lymphosarcoma of the mediastinum, and (5) adenocarcinoma of the stomach. Only in Case 3 was esophageal hiatus hernia the primary diagnosis. To obtain a series such as the one reported requires a serious survey of surgical records, and it is hoped that additional series may soon be forthcoming.

It should be emphasized that a decision to treat esophageal hiatus hernia with less than hernioplasty must be accompanied by an appreciation of the risks involved. This report is not a statistical survey, and it is not possible to state how often catastrophies occur. Obviously they occur often enough to permit a series such as this to be compiled without too much difficulty. This is particularly significant in view of Sweet's recent statistical report on transthoracic hiatus hernioplasty with no fatalities in over 100 cases.[7]

CONCLUSIONS

1. When an esophageal hiatus hernia causes symptoms, surgical intervention is indicated. Failure to treat symptomatic hiatus hernias by operation may result in complications which, if not fatal, may threaten life.

2. The specific treatment of esophageal hiatus hernia is hernioplasty by either the thoracic or the abdominal route.

3. Phrenicoexeresis plus medical management is the minimal procedure in cases not suitable for hiatus hernioplasty.

TREATMENT OF PERFORATED PEPTIC ULCER

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DURING recent years two new methods have been developed for treatment of perforated gastric or duodenal ulcers: primary subtotal gastrectomy and conservative therapy without surgical intervention. The marked fall in the mortality figures for gastric resection which has occurred during recent years has induced some surgeons to employ this procedure in certain of their patients with perforated ulcer. Owing to the effect of antibiotics, blood transfusions, and adequate parenteral administration of fluids combined with continuous suction through an indwelling stomach tube, conservative therapy without surgical intervention has been successfully used in treating the same disorder.

TABLE 1.—*Number of Patients Admitted from January, 1942, to July, 1951, with Deaths**

Yr.	Patients	Deaths	Mortality Rate
1942	2	0	....
1943	4	2	....
1944	6	1	....
1945	3	1	....
1946	4	2	....
1947	13	0	....
1948	15	1 (+1)	....
1949	12	1 (+1)	....
1950	16	2	....
1951 (Jan.-June)	4	0	....
1942-46	19	6	31.6
1947-51	60	4 (+2)	6.7
1942-51	79	10 (+2)	12.7 (15.2)

* The figures in parentheses indicate preoperative deaths and the preoperative mortality rate, if these are included.

I have had no experience with the latter method of treatment, but through a follow-up study of our patients at Central Hospital I am able to give an opinion on the use of primary gastrectomy, for which reason I publish the following report. The series presented consists of all the patients who were treated for perforated gastric or duodenal ulcers in the surgical clinic of this hospital from January, 1942, to July, 1951, the period during which a special surgical clinic has been in existence in Randers, Denmark. All the patients except two, who entered the hospital in a moribund condition and died shortly after admission despite therapeutic measures, were treated with simple suture.

During the first five years the number of patients with perforated ulcer varied from 2 to 6 annually; during the last five years it varied from 8 (1951) to 16

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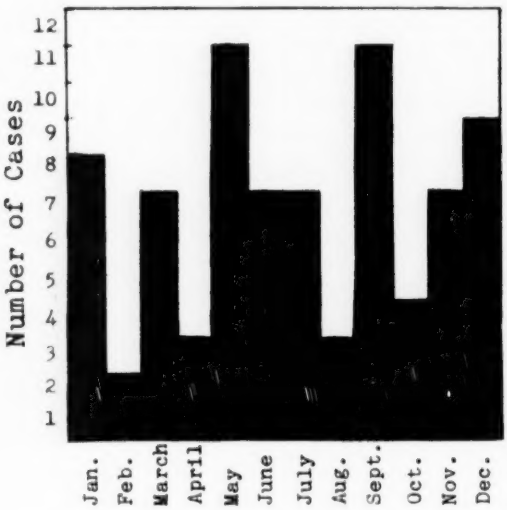
annually. As in all other reports published during recent years, the mortality shows a decreasing trend, which must be attributed chiefly to adequate treatment before and after operation with transfusions, antibiotics, and so on.

Of the 79 patients 6 were women, i. e., 7.6% (approximately one-thirteenth). Two of these six died (1 before operation), the mortality rate thus being 33.3% (preoperative, 16.7%), while the death rate among the men was 13.7% (preoperative, 12.3%). The ages of the patients ranged from 77 (a man) to 16 (a girl).

One patient who was operated upon for duodenal ulcer returned two years later with a second perforation.

Of 61 patients operated on (including 11 of the 12 who died) for whom the duration of the perforation could be ascertained, this was 5.3 hours for the survivors and 13.1 hours for those who died. The duration of the perforations among the



Occurrence of perforation in relation to season of the year.

survivors ranged from 1 to 29 hours; among those who died it ranged from 4 to 48 hours.

The time when the perforations occurred as related to the season of the year is shown in the accompanying chart. The largest number of perforations occurred during May and September and the smallest number during February, April, and August. Such peaks during spring and fall have been demonstrated by many writers and seem to be the rule.

The distribution of the ulcers according to site appears in Table 2; there were 20 perforations of duodenal and 59 perforations of gastric and pyloric ulcers. This distribution is not in agreement with that usually seen now for gastric and duodenal ulcers in men and women. As is well known, the duodenum is by far the most common site of ulcer. Before and about 1920 the distribution of gastric and duodenal ulcers occurring among the population of Copenhagen, Denmark, showed that the vast majority were found in the stomach, while duodenal ulcers had a

much lower incidence. On the other hand, during more recent years most ulcers have occurred in the duodenum, both in men and in women. Thus, in 1935 Alsted [1] found 109 duodenal ulcers as compared with 11 at the pylorus and 11 on the lesser curvature.

The distribution of our perforated ulcers suggests that prepyloric and gastric ulcers have a higher tendency to perforation than duodenal ulcers (59 as opposed to 20). It has been shown by Alsted that during 1911-1915 perforation was only three times as frequent in men as in women. During 1931-1935 the corresponding ratio was 13:1, which is, incidentally, the same as that in our series. This change presumably is due mainly to the fact that peptic ulcer among women has shown a downward trend during the years.

For some time I have noticed that when patients who have undergone operation for gastric ulcer enter the hospital for another operation, the second ulcer is often not located at the site of the first perforation but is usually more distal and is most

TABLE 2.—*Distribution of the Ulcers According to Site and Sex*

	Prepyloric Region	Duodenum	Lesser Curvature	Pylorus
Men	35	20	11	7
Women	3	..	3	..

TABLE 3.—*Site of the Ulcer at Second Operation*

Perforation	Duodenal	Pyloric	Gastric or Prepyloric	No Ulcer
10 gastric or prepyloric	5	2	2	1
1 pyloric	..	1	..	..
2 duodenal	1	1	..	..

frequently in the duodenum. For this reason I have analyzed the cases in which a second operation was performed for peptic ulcer. Of 14 patients, 13 underwent gastric resection at the second operation (with one death), and one had vagotomy and anastomosis.

In 10 cases the perforation was prepyloric or gastric. The second operation revealed that the second symptom-producing ulcer was situated in the duodenum in five cases and in the pylorus in two cases; no ulcer was found in one case, although the roentgenogram had shown duodenal ulcer, and ulcerations were seen both in the stomach and in the duodenum in one case. In one case the perforation was situated in the pylorus; at the second operation the ulcer was found in the pylorus, although the roentgenogram had shown duodenal ulcer. In two cases the perforation was located in the duodenum; a second operation revealed ulcer of the pylorus in one case and ulcer of the duodenum in the other. Roentgenograms had in both cases shown duodenal ulcer. In the last of the 14 cases the perforation occurred in the middle of the lesser curvature. The second operation consisted of

1. Alsted, G.: Studies on the Changing Incidence of Peptic Ulcer of the Stomach and Duodenum, Copenhagen, Ejnar Munksgaards Forlag, 1939.

vagotomy plus a new anastomosis, because an anastomosis performed before the perforation had become occluded. Numerous old adhesions, which masked the picture, were found.

My observation with regard to the change in the site of the ulcer was further confirmed by the findings revealed at the follow-up examination of patients who had unquestionable roentgenologic signs of duodenal ulcer. Admittedly, the roentgen examination revealed duodenal ulcer in 4 cases in which the perforation had occurred in the duodenum; but of 13 cases in which the perforation had been located in the prepyloric region or on the stomach, roentgenograms at the follow-up examination showed ulceration of the duodenum in 11 cases and of both the stomach and the duodenum in 2 cases. In one case of perforation of the pylorus there was now evidence of duodenal ulcer. In only one case of perforated duodenal ulcer did subsequent roentgen examination reveal a new ulceration on the lesser curvature of the stomach.

TABLE 4.—*Subsequent Site of Ulcer at Roentgen Examination*

Perforation	Duodenal	Pyloric	Gastric or Prepyloric	Gastric or Duodenal
13 gastric or prepyloric	11	..	..	2
1 pyloric	1	..	..	..
4 duodenal	4	..	..	..

TABLE 5.—*Subsequent Course in Cases of Perforated Ulcers*

	Cases
Primary death	12
Subsequent death	2
Second operation	14
Personal examination	46
Examination by questionnaire	4
No examination	1
Total	79

These findings confirm the observation that in patients who have been operated upon for perforated ulcer and later have symptoms of a new ulcer, the second ulcer most frequently occurs in a site different from the original one; most commonly, a perforated prepyloric ulcer is followed by a symptom-producing duodenal ulcer. In some cases an apparent change in site may be ascribed to incorrect localization of the ulcer at the operation for perforation; it is occasionally difficult to decide whether an ulcer is situated proximal or distal to the pylorus, owing to the surrounding, often edematous, thickened tissue. But in other cases, in which the perforation occurred in the higher portions of the stomach, it was beyond doubt that the site of the new ulcer differed from that of the first. This is an interesting observation, although it is of less practical than theoretical importance, since the patients, nevertheless, should be gastrectomized.

Table 5 summarizes the subsequent course in the 79 cases of peptic ulcer. Of the 79 patients, 12 died of the perforation. One patient, a 76-year-old man, died of hematemesis at the medical department three weeks after discharge; another patient later committed suicide.

As already stated, 14 patients underwent a second operation; 46 were examined in person, and 4 answered a questionnaire. One could not be traced. Thus, exclusive of those subjected to a second operation, we have been in touch with 50 patients of 51 possibilities. The results of the follow-up examinations appear in Table 6.

The group with "severe symptoms" includes the 14 patients who later underwent a second operation. All of them had severe dyspepsia. (In one of them a tumor was, however, suspected; another was operated upon also because of repeated hematemesis.) Thus, at the follow-up examination six months to nine years after the perforation, 20% of the patients were free of symptoms, 42% had mild symptoms (both groups, however, having been restored to full working capacity), and 38% had severe symptoms.

TABLE 6.—*Results of Follow-up Examinations*

Perforations	No Symptoms	Mild Symptoms	Severe Symptoms
Gastric or prepyloric, 43 (68%)	8 (19%)	17 (40%)	17 (40%)
Pyloric, 5 (7%)	.....	3	2
Duodenal, 16 (25%)	5 (31%)	7 (38%)	5 (31%)
Total, 64	13 (20%)	27 (42%)	24 (38%)

TABLE 7.—*Survey of Results Obtained by Various Writers*

Author	No. of Cases Followed Up	Good Result, %	Medium Result, %	Poor Result, %
Abrahamsen,[2] 1925	56	52	27	21
Bager (Acta chir. scandinav., Supp. 11, **64**:5, 1929)	318	43	13	44
Morville,[4] 1930	41	20	22	58
Kühnel,[5] 1930	28	25	43	32
Sørensen,[6] 1951	44	25	21	54
Kingsbury and Peacock (Surg., Gynec. & Obst. **92**:717, 1951)	70	45	..	..
Tovee,[8] 1951	78	23	30	47
Lassen, 1952	64	20	42	38

Table 7 contains a survey of the results obtained by various Scandinavian writers supplemented by two recent American reports.

It appears that after simple suture of a perforated ulcer nearly two-fifths of the patients have symptoms so severe that they are seriously troubled by their disease and at least periodically incapacitated. On the other hand, slightly more than one-fifth are free of symptoms and apparently completely cured, and for these simple suture is adequate. Inadequacy of the suture was not encountered in any of the cases discussed here.

Of the women, one was free of symptoms, two had mild symptoms, and one had severe symptoms. As in most other reports, the figures are too small to allow any definite comparison, but they seem to confirm the opinion expressed by others that the subsequent course is less favorable in women than in men.

Also with regard to the site of the ulcers, the figures are too small to allow definite conclusions as to the prognosis of the various ulcers. According to the present series the prognoses for perforated gastric and duodenal ulcers seem to be

almost equally good. Other reports indicate that perforations of gastric ulcer have a poorer prognosis, although in Abrahamsen's [2] series they showed a better prognosis.

Of the 46 patients who appeared for follow-up examination, 45 had roentgen examinations. In many cases the roentgen findings showed good agreement with other clinical observations and possible operative findings, but roentgen examination has certain limitations and it is difficult to assess the films. Gastritis or gastroduodenitis was often demonstrated, but irregularities around the duodenal bulb and the pylorus due to adhesions, contraction of scar tissue, or spasms made it difficult to decide whether or not an ulcer was present. Accordingly, the roentgen diagnosis was often one of doubtful ulcer.

It may be asked how often a second operation is indicated for previously treated perforated peptic ulcer with simple suture. Table 6 shows that among our 64 patients who were followed up, 24 actually should have been operated on again if only the severe symptoms displayed at the follow-up examination were taken into account. Some of them were so old (or so young), however, that another operation was scarcely indicated in spite of their severe symptoms. Moreover, various writers, including Tovee,[3] have shown that even though patients may have typical, fairly severe symptoms of ulcer 1 to 3 years after a perforation, they may well be symptom-free, for example, 10 years after the operation. In view of this observation the surgeon should not be too anxious to employ primary or secondary resection.

The possibility of hematemesis should be considered. Two patients had hematemesis some time after the suture operation. One of them, a 76-year-old man, died of it at the medical department three weeks after discharge from the surgical clinic (1944). The other, a 32-year-old man, had hematemesis several times two years after the suture operation; he was gastrectomized and recovered.

Several writers have pointed out that it is often difficult to ascertain from highly distressed patients who enter the hospital with a perforated ulcer how long dyspeptic symptoms have persisted before the perforation. For this reason one cannot rely on the pertinent information of the hospital record; nor does a questionnaire give exact information as to this point or as to the condition of the patient after the operation. A personal examination is highly preferable, but even this method may fail in its purpose. Thus, one of our patients stated at the follow-up examination that he had no symptoms whatever; an accidental interview with his wife shortly afterward revealed that he had frequent, fairly severe symptoms but had not disclosed them for fear of a second operation.

Among the 64 patients subjected to follow-up examination, the perforation had occurred suddenly, without any preceding symptoms, in 6. In Morville's [4] series only 3 among 44 followed up had this type of onset. Among Kühnel's [5] patients there were none who had not had symptoms for at least a few days prior to the perforation. Bent Sørensen found 7 without preceding symptoms among 43 patients.

As may be seen from Table 6, a prognosis cannot with certainty be made on the basis of the site of the ulcer. On the other hand, a comparison of the prognosis

2. Abrahamsen, H.: Hospitalstid. **68**:367, 1925.

3. Tovee, E. B.: A. M. A. Arch. Surg. **63**:408, 1951.

4. Morville, P.: Hospitalstid. **73**:315, 1930.

5. Kühnel, P.: Hospitalstid. **73**:849, 1930.

for the patients in whom the symptoms prior to the perforation were of only short duration (up to one month) with that for the patients with symptoms of longer duration shows that subsequent severe symptoms developed twice as frequently in patients with long-standing symptoms as in those with symptoms of only short duration (Table 8).

The same relationship is seen in several other reports, for example those published by Abrahamsen,[2] Bent Sørensen,[6] and Luer,[7] while some investigators do not find such a correlation.

If certain recognized criteria for primary subtotal gastrectomy in the treatment of perforated ulcer had been applied to our series, viz., patients between the ages of 30 and 50 with at least a five-year history of peptic ulcer and in a good general condition, 20 patients (about 25%) would have been subjected to this operation (Table 9, Section I). Of these 20, severe symptoms later developed in 3 and

TABLE 8.—*Relationship of the Duration of Symptoms Before the Perforation to Later Symptoms*

Duration of Symptoms Before Perforation	No Symptoms	Mild Symptoms	Severe Symptoms	Subsequent Operation
Less than 1 mo.	5	6	2	1
			3 (21%)	
Long-standing symptoms	8	20	9	13
			22 (44%)	

TABLE 9.—*Analysis of Cases According to Criteria for Primary Gastrectomy*

	Severe Symptoms	Mild Symptoms	No Symptoms	Not Followed Up	Secondary Gastrectomy
I. Ulcer history of at least 5-yr. duration Age: 30-50 yr. 20 patients (approx. 25%)	3	7	2	1	7
II. Ulcer history of at least 12-mo. duration Age: 25-55 yr. 39 patients (approx. 50%)	6	17	5	1	10

mild symptoms in 7, while 2 had no later symptoms, 1 was not followed up, and 7 were subjected to secondary resection.

As will be seen, only 7 of our 14 patients subjected to a secondary operation fell within this group. We would have subjected to resection two patients who were completely free of symptoms, seven with symptoms so mild that they were fully capacitated, and only seven with severe symptoms.

Incidentally, if primary resection were to be advocated, I find that it would be justifiable to extend the age limits to, for example, 25 to 55 or 60 years.

If the indications for primary resection had been extended so that all patients between the ages of 25 and 55 years with an ulcer history of at least 12 months' duration were included, the number of primary gastrectomies would (as appears from Table 9, Section II) have been increased from 20 to 39. Included would have been 3 more patients with subsequent severe symptoms, 3 more who would

6. Sørensen, B.: Ugesk. læger **113**:991, 1951.

7. Luer, C. A.: Surgery **27**:360, 1950.

have had resection according to the aforementioned criteria, but, unfortunately, also 3 more who later remained symptom-free, and 10 more who had only mild symptoms.

Thus, it is seen that it is scarcely possible to set forth criteria for the use of primary gastrectomy for perforated peptic ulcer without including too many patients with no or only mild subsequent symptoms and too few with severe symptoms.

The average age of the patients who were free of symptoms at the follow-up examination was 40 years and that of the patients with severe symptoms 43 years, which is only an insignificant difference. Two of the youngest patients, 16 and 22 years old, were in the group with severe symptoms.

The average age of the entire series was 45 years as compared with an average age of 58.4 years for the patients who died.

It must be admitted that gastrectomy performed secondarily after a suture operation for perforated ulcer is often a difficult procedure, although the difficulties we encountered do not seem to have been so great as those described in some other reports. However, one death occurred among the 14 patients subjected to a second operation.

COMMENT

The methods of treatment available for patients with perforated peptic ulcers are either entirely conservative—without surgical intervention, with continuous suction through an indwelling stomach tube, a strict dietary regimen, blood transfusion, restoration of the fluid and electrolyte balance, and antibiotic therapy—or simple suture of the ulcer, excision of the ulcer plus closure, suture plus gastroenteroanastomosis, and, finally, primary subtotal gastrectomy.

Many physicians find that the entirely conservative method gives very good results, although some writers have reported results essentially inferior to those obtained by the suture operation. The suction method has in some cases saved the lives of patients who were in such a poor condition that operation was out of the question. Likewise, this method is useful as a preoperative measure, since some patients who could not immediately withstand operation may be rendered fit for operation in a few hours. Where the facilities for operation are poor, for example on board ships in the open sea, the suction method should certainly be borne in mind. In view of my studies of the literature, however, I dare not recommend this procedure as a standard method. It should presumably be used chiefly as a preliminary measure for patients who are so severely affected that they cannot stand immediate operation.

Suture of the ulcer, with gastroenterostomy, will scarcely be recommended today from any quarter as a standard method but should be reserved for cases in which it is feared that the suture will result in pyloric stenosis. Excision with ensuing closure is hardly used any more. The choice must be between simple suture and primary subtotal gastrectomy.

In our hospital technical facilities for primary gastrectomy are practically always present. Nevertheless, I do not advocate this measure, because, as shown in my account, gastrectomy would inevitably be performed on some patients in whom subsequent symptoms of ulcer would not develop and on a large number of patients who are fully capacitated even though they may suffer—often only occa-

sionally—from slight dyspepsia. Furthermore, my account has shown that even if the indications for primary resection were considerably extended, the operation would not be performed on many patients who would later require it.

I intend in future to use primary simple suture in our clinic and to recommend that gastrectomy be performed secondarily when required. In my opinion, primary resection for perforated ulcer is advisable only if this procedure insures a lower mortality than if primary suture and secondary resection when required are employed. A sufficiently large case material of a nature to elucidate the problems involved has not yet been published.

A large number of unsolved problems are attached to the causation of peptic ulcers. Since 1920 a change in the incidence and localization of such ulcers has occurred in all parts of the world; duodenal ulcers are now by far the commonest, although gastric ulcers still show the greatest tendency to perforation. Furthermore, I am at a loss to explain the observation demonstrated in this report that perforated gastric ulcers most frequently disappear after simple suture and subsequent ulcer symptoms if they appear usually originate from duodenal ulcers which have developed later. In all parts of the world, notably in Scandinavia, the incidence of perforated ulcers has shown a marked increase during recent years.

If these problems and several other peculiarities associated with peptic ulcers had not until now defied solution, we would be better equipped to understand prophylactic measures against and treatment of these lesions.

SUMMARY

From a central hospital in Denmark a case material of perforated peptic ulcers covering a period of nine and one-half years is presented. A follow-up study of 64 patients (98.5%) of 65 possibilities is reported. It is demonstrated that gastric ulcers have a greater tendency to perforation than duodenal ulcers.

Evidence is presented in support of the observation that perforated prepyloric ulcers in patients in whom ulcer symptoms later develop are replaced by symptom-producing duodenal ulcers, while the original perforation has healed. As far as is known, this observation has not previously been reported.

Absolute criteria for primary partial gastrectomy for perforated ulcer cannot be set forth, since this operation would then inevitably be performed on some patients in whom subsequent ulcer symptoms would never have developed and yet would not be performed on all those in whom severe symptoms requiring secondary resection would develop.

Simple suture, possibly followed by secondary partial gastrectomy, if the latter measure is indicated by subsequent severe symptoms, is therefore recommended as the standard method of operation.

ENDOMETRIOSIS OF THE VERMIFORM APPENDIX

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AFTER the publication of an article by Collins entitled, "Endometriosis of the Vermiform Appendix: Review of Literature, with Addition of Nine New Instances, One of Which Caused Severe Melena," which appeared in the A. M. A. ARCHIVES,[1] it now seems opportune to report five of my own cases. They had other types of clinical findings than those reported by Collins, though the endometrial tissue had the same unusual location.

In 1932 to 1933, operations for endometriosis of the appendix were carried out in four cases, at the Maria Hospital, headed at that time by Prof. E. Key. In 1935 I made a short report to the Swedish Surgical Association of these and 31 other cases collected from the literature. Most of the latter are included in Collins' review, but reference to his footnotes shows that he failed to mention 11 cases. These 11 cases, my four, and another one passed on to me in connection with my report of 1935 (in which treatment was given by Dr. L. Simon, Norrköping) should therefore be added to Collins' collection of 134 to bring the total to 150 cases.

The data are from the extra 16 cases, which include 11 from the literature and five of my own cases. The average age in 13 reported instances was 37.38 years. The marital status in 11 reported cases was 1 single person and 10 married persons (7 of these had 11 children). The location of the endometrial lesion in the appendix was at the tip in six cases and between the tip and the base in one case. No data were given in 8 cases. The associated pathological findings included marked endometriosis of the right pelvic adnexa in six cases and an apparently normal right adnexa in three cases. Inexact data were given in seven cases.

My five cases provide good examples of two main varieties of the clinical picture met with in endometriosis of the appendix. In three cases the preoperative diagnosis of acute appendicitis had been made. In two of these, a right-sided adnexal endometriosis was found which had given rise to dysmenorrhea and chronic discomfort. The actual acute symptoms were due to the rupture of a chocolate cyst. The concurrent endometriosis of the appendix had scarcely given rise to any symptoms. In the third case a ruptured chocolate cyst together with endometriosis in the appendix was found with signs of both chronic and suppurative appendicitis. In the two other cases recurrent attacks of fever and abdominal pain led to the preoperative diagnosis of myoma in a state of degenerative change. In both cases

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1. Collins, D. C.: Endometriosis of the Vermiform Appendix, A. M. A. Arch. Surg. **63**:617-622, 1951.

the adnexa were normal. In the first case a necrotic myoma containing endometrial tissue was enucleated. In addition to an endometriosis involving the appendix, a small abscess was also found encircling the latter, in the wall of which were seen chronic inflammatory changes. The appendix had therefore been the seat of recurrent infection, and an abscess had earlier burst into the rectum. In the second of these two cases, the uterus, showing myomatous changes, was amputated. Microscopy revealed a fibromyoma with regressive changes. The appendix, free and slightly kinked at the apex, was extirpated *en passant*. At microscopy an obliterated lumen, probably the result of an old healed infection, was seen. Endometrial tissue was found at the tip.

COMMENT

In the first two cases the endometriosis of the appendix was an accidental finding of no significance. This fact may also be true in the next two cases in which appendicitis was the main feature. In at least one of the latter two cases, however, the endometriosis of the appendix played a definite role in determining the course and complications of the appendicular infection. It cannot be decided whether the endometriosis had any significance in the development of the appendicitis in these two cases (and the old chronic infection in the last one). Nevertheless, it is conceivable that an appendix infiltrated by an endometriosis should be a more likely seat of inflammation than a normal one.

The last case is notable for the fact that any endometrial tissue present was found located in the appendix and nowhere else. More than likely this condition underlay the recurrent right-sided pains accompanying menstruation and disappearing after operation. Similar, but even more marked, recurrent pains of the appendicular colic type are described [2] in a case with a stenosing endometrial infiltration encircling the appendix near its base.

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CAUSE OF SURVIVAL OF DOGS WITHOUT A HEPATIC ARTERY

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THE HEPATIC artery contributes about 20% of hepatic blood flow, while the portal vein carries the remaining 80%. There is some collateral supply, but under normal conditions this is negligible. Reciprocal variations in the amount of blood carried by either the hepatic artery or the portal vein occur, and Soskin and co-workers [1] have observed that this reciprocal variation could be as low as 10% or as high as 90% in either vessel.

Some interesting observations have been made when the liver is supplied by either one of these vessels, the other being tied. Ligation of the portal vein, as in Eck fistula, results in parenchymal fibrosis and considerable reduction in the size of the liver. The dogs, however, do not die, and there is little or no alteration in hepatic function.[2] Ligation of all the branches of the hepatic artery is followed in about 100% of cases by a peculiar stinking and gassy necrosis resulting in death 15 to 50 hours postoperatively.[3] This observation has been repeated more recently by various workers [4] and confirmed in the experiments presented here. With the exception of the rat the same observation has been made in other animals and in man.[5]

From the Department of Physiology, University of Toronto.

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3. (*a*) Haberer, H.: Experimentelle Unterbindung der Leberarterie, Arch. klin. Chir **78**:557, 1905. (*b*) Harrison, G. A.: Chemical Methods in Clinical Medicine: Their Application and Interpretation with the Technique of the Simple Tests, Ed. 2, London, J. & A. Churchill, Ltd., 1937. (*c*) Huggins, C., and Post, J.: Experimental Subtotal Ligation of the Arteries Supplying the Liver, Arch. Surg. **35**:1165, 1937. (*d*) Narath, A.: Über Entstehung der anämischen Lebernekrose nach Unterbindung der Arteria hepatica und ihre Verhütung durch arterio-portale Anastomose, Deutsche Ztschr. Chir. **135**:375, 1916.

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In 1916 Narath [3d] observed that three of seven dogs survived anastomosis of the hepatic artery to the portal vein, one dog living as long as 62 days. He concluded that the hepatic necrosis on ligating the hepatic artery was due to lack of arterial blood. Following up this important conclusion, Markowitz and co-workers tried to repeat this observation by arterializing the portal blood by various means after effective ligation of the hepatic artery.[4e] They obtained conflicting results. Assuming the inadequacy of their aseptic facilities, they tried to improve the postoperative recovery of their dogs by giving them penicillin. To their surprise a large number of the dogs survived effective ligation. At postmortem examination, however, they found that the anastomotic site was thrombosed, that no arterial blood was entering the portal vein, and that the liver was normal. To eliminate all variables, they observed two groups of dogs with ligated hepatic arteries, one receiving and the other not receiving doses of penicillin. They made the observation that penicillin prevents the hepatic necrosis, which is almost always fatal following ligation of the hepatic artery. Markowitz and co-workers believe that the necrosis is bacterial, and, since it follows arterial ligation but not portal ligation, that the bacterial proliferation is anaerobic. The function of the hepatic artery in the normal dog is to maintain a high oxygen tension to discourage the proliferation of anaerobes, which bring about most, if not all, of the necrosis. After confirmation of this observation by other workers, various explanations have been offered as to why antibiotics need not be given indefinitely for survival. Tanturi and others [4f] associate the necrosis with lecithinase. This enzyme normally is not found in the blood.[6] In the peritoneal fluid, which always accompanies liver peritonitis, they observed lecithinase activity. Lecithinase has been identified with the α-toxin of Clostridium perfringens Type A. It is their belief that antibiotics abort the disease process by destroying certain bacteria present in the exudate, thus preventing the synergistic growth necessary for the production of metabolites required for the production of lethal enzymes. Fraser [4a] postulates a primary ischemic necrosis and secondary bacterial activity with further massive necrosis. Grindlay and his associates [4b] attribute the survival of their penicillin-treated dogs to revascularization.

PURPOSE

The purpose of this research was to study the effects of giving one small (inadequate) dose of penicillin to a dog after ligation of the hepatic artery. It was our hope to produce a small scarred liver after a stormy convalescence. In this we failed but observed another fact of consequence, the object of this report.

METHODS

The investigations were carried out on apparently healthy dogs weighing from 8 to 16 kg. Complete ligation of all the arterial vessels supplying the liver was carried out with the animal under pentobarbital calcium (nembutal®) anesthesia and with use of climbing ligatures, as described by Markowitz and others.[4c] In view of the reported toxic effects of meat extrac-

6. MacLennan, J. D., and MacFarlane, R. G.: Toxin Antitoxin Studies of Gas-Gangrene in Man, Lancet **249**:301, 1945.

tives following liver injury [7] all the dogs received a meat-free diet 2 days before and 12 days after operation. The diet consisted of the following:

Powdered milk sugar	40 gm.
Brown bread	300 gm.
Mineral salt mixture	2 gm.
National dried brewers' yeast	2 gm.

Enough water was added to this mixture to make a pasty consistency. From the 13th postoperative day the dogs were fed with the normal laboratory stock diet.

The dogs were divided into the following two groups: Group A, those given no penicillin, Dogs 12, 18, and 22, and Group B, those treated with penicillin, Dogs 7, 11, 14, 15, 16, 26, 27, 30, and 32.

Each dog in Group B received only one subcutaneous injection of 100,000 units of penicillin G potassium immediately after the ligation.

Various biochemical determinations were made on most of the dogs in order to follow hepatic changes and determine survival of the operation. The following liver function tests were carried out [8] (Table 1).

TABLE 1.—*Liver Function Tests*

Test	Method	Modification
Sulfobromophthalein sodium excretion	Rosenthal and white [8f]	Standard curve, 5 mg./kg.
Plasma bilirubin (direct and indirect)	Malloy and Evelyn [8c]	Schiff [8g]
Urine albumin	Esbachs [8b]	.....
Urinary bilirubin	Harrison [8h]	.....
Urine sugar	Benedict [8a]	.....
Blood sugar	Nelson [8d]	Somogyi [8e]

TABLE 2.—*Data on Dogs Given No Penicillin*

Dog No.	Weight, Kg.	Date of Operation	Survival	Comment
12	14.3	10/24/51	36 hr.	Liver necrosis
18	13.5	12/10/51	25 hr.	Liver necrosis
22	13	12/17/51	24 hr.	Liver necrosis

RESULTS

The dogs injected with penicillin nearly always lived; the others uniformly died.

No biochemical tests were carried out on these dogs. At autopsy the gross findings were similar. The stomach was distended. When the abdominal cavity

7. Bollman, J. L.: The Influence of Diet on the Production of Ascites, Arch. Path. **6**:162, 1928.

8. (*a*) Benedict, S. R.: The Detection and Estimation of Glucose in Urine, J. A. M. A. **57**:1193, 1911. (*b*) Esbach, H.: Urine Protein, in Hawk, P. B.; Oser, B. R., and Summerson, W. H.: Practical Physiological Chemistry, Philadelphia, The Blakiston Company, 1947, p. 868. (*c*) Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481, 1937. (*d*) Nelson, N.: A Photometric Adaptation of the Somogyi Method for the Determination of Glucose, ibid. **153**:375, 1944. (*e*) Somogyi, M.: A New Reagent for the Determination of Sugars, ibid. **160**:61, 1945. (*f*) Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112, 1925. (*g*) Schiff, L.: The Differential Diagnosis of Jaundice, Chicago, The Year Book Publishers, Inc., 1946. (*h*) Harrison.[8b]

was opened it discharged a puff of foul-smelling gas. Dark-colored fluid was found in the abdominal and chest cavities. The liver capsule was mottled and sloughed in places, especially the left lobes. The liver substance was soft to touch. There was generalized hepatic necrosis. Abscesses were found at the tip of the quadrate lobe and at the root of the gall bladder. The gall bladder was soft and edematous, and in Dog 12 (not given penicillin) the gall bladder was perforated. The gastrohepatic omentum showed gangrenous necrosis. Histological examination showed an advanced or complete cell lysis. There was widespread and unresolved centrolobular necrosis (Fig. 1).

Penicillin-Treated Dog 7.—This dog appeared normal five days postoperatively. On the sixth day it showed signs of weakness and loss of appetite, with squatting on the hind legs all the time. On the seventh day the condition was not improved, and it died in the night. Because of postmortem changes that must have taken place, no histological specimens were taken.

TABLE 3.—*Data on Penicillin-Treated Dogs*

Dog No.	Weight, Kg.	Date of Operation	Survival, Days	Comment
7	16	10/10/51	7	Died in the night 10/17/51; acute biliary peritonitis; gangrenous necrosis of gastrohepatic omentum; dark stinking fluid in peritoneal cavity; necrosis of left hepatic lobes; possibly postmortem changes contributed to the above
11	12.6	10/24/51	13	Killed 11/6/51 when distemper developed; postnecrotic repair and regeneration of early postoperative necrosis
14	13.5	11/14/51	63	Killed 1/14/52; liver parenchyma normal
15	14.5	11/14/51	112	Still alive
16	16.6	11/15/51	56	Killed 1/9/52; liver parenchyma grossly normal
26	9.5	1/18/52	12	Killed 1/30/52; liver parenchyma essentially normal
27	9.5	1/18/52	17	Killed 2/4/52; liver parenchyma grossly normal
30	8.5	1/28/52	7	Killed 2/4/52; small foci of ectopic cells indicating mild necrosis had occurred before but repair was complete
32	15	2/ 1/52	3	Areas of necrosis at tip of the left medial lobe; otherwise, liver essentially normal

Gross observation revealed acute biliary peritonitis. The left hepatic lobes were soft and hemorrhagic. There was a gangrenous necrosis of the gastrohepatic omentum, and a dark-colored stinking fluid was found in the peritoneal and chest cavities.

Penicillin-Treated Dog 11.—This dog showed signs of recovery on the third postoperative day. Biochemical studies, however, showed impaired liver function until the sixth day, returning to normal on the eighth. There was a rise in sulfobromophthalein sodium retention and plasma bilirubin on the 10th day. The blood sugar was relatively normal all the time. On the 12th day the dog was observed to be suffering from distemper and was killed the following day.

On postmortem examination a small quantity of fluid was seen in the abdominal cavity. The left medial lobe showed signs of necrosis and sclerosis, and pus had developed at the neck of this lobe. The tip of the quadrate lobe was sclerotic. The gall bladder was perforated and necrotic. There was widespread centrolobular necrosis during the immediate postoperative period. At autopsy, however, active necrosis was absent and active postnecrotic repair and regeneration were present (Fig. 2).

Fig. 1 (Dog 18, no penicillin treatment).—Photomicrograph showing extensive coagulative necrosis. Even portal triad has (lower left) undergone degeneration. This dog died in 25 hours Hematoxylin and eosin stain; × 120.

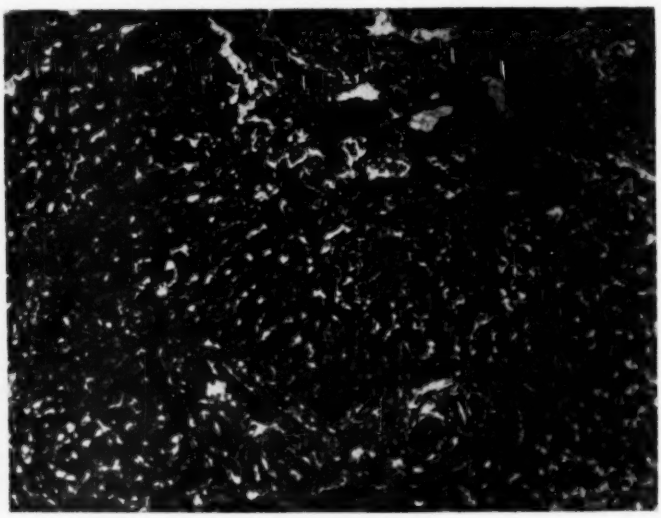

Fig. 2 (Dog 11, treated with penicillin).—Photomicrograph showing central necrosis (upper right) and normal periportal tissue. This dog received 100,000 units of penicilllin G potassium Distemper developed, and the dog was killed on the 13th postoperative day.

Fig. 3 (Dog 14, treated with penicillin).—Photomicrograph showing relatively normal liver parenchyma. This dog received 100,000 units of penicillin G potassium. Eight weeks postoperatively, this dog was killed. Hematoxylin and eosin stain; × 80.

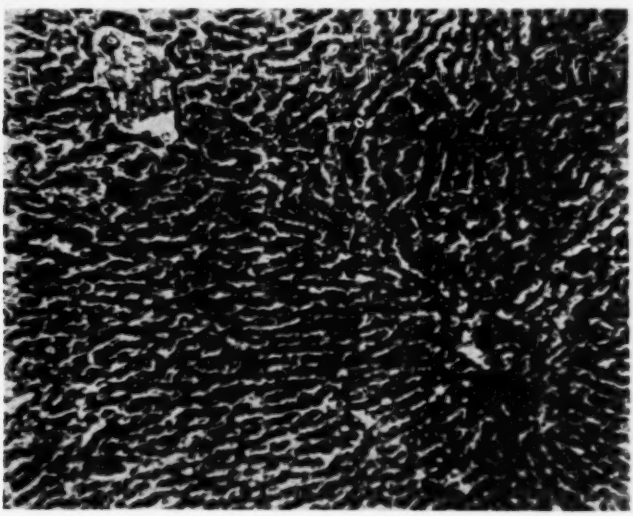

Fig. 4 (Dog 30, treated with penicillin).—Photomicrograph showing relatively normal periportal tissue. One dose of penicillin G potassium was given to this dog. The dog was killed seven days postoperatively. Hematoxylin and eosin stain; × 80.

Penicillin-Treated Dogs 14 and 16.—These two dogs lived for nine and eight weeks, respectively, before autopsy. Liver dysfunction was apparent on the 2d postoperative day, rising to a maximum on the 5th and 7th days but returning to normal on the 8th and 11th days. There was high plasma bilirubin and high sulfobromophthalein sodium retention in Dog 14 between the 27th and the 36th day postoperatively, but there was a return to normal on the 42d day, and no further abnormalities were observed after that.

At autopsy the liver and other abdominal organs were normal. The gall bladder was atrophic and the area covered by dense fibrous adhesions. The right medial and caudate lobes were adherent to the duodenum and gastrohepatic omentum. The right and left medial lobes were adherent to the diaphragm, and on severing there was bleeding. Histological examination showed normal liver parenchyma (Fig. 3).

Fig. 5 (Dog 32, treated with penicillin).—Photomicrograph showing normal periportal tissue (center). Some centrolobular necrosis is present (upper right and lower left corners).

Penicillin-Treated Dog 26.—This dog showed hepatic insufficiency from the second postoperative day, reaching a maximum on the fourth day, with a return to normal on the sixth day.

Autopsy disclosed that the liver and other abdominal organs were normal. The left median and right median lobes were adherent to the diaphragm and the right lateral and caudate lobes to the duodenum and gastrohepatic omentum. The gall bladder was atrophic, and the area was covered by dense fibrous adhesions. Histologically, the liver was essentially normal. Small areas or foci indicated previous hemorrhage. There were signs of atrophy of the portal triads and preautopsy deposition of a large amount of glycogen.

Penicillin-Treated Dog 27.—This dog showed poor liver function from the second postoperative day, reaching a maximum on the fourth, with a gradual return to normal on the ninth day.

At autopsy the liver and other abdominal organs were normal. The gall bladder was completely embedded between the right medial and quadrate lobes and was sclerotic. The caudate, right medial, and lateral lobes were adherent to the duodenum and greater omentum.

Penicillin-Treated Dog 30.—In this dog hepatic insufficiency was apparent the day after operation, reaching a maximum on the third day and returning to normal on the sixth day (Fig. 4).

At autopsy the liver and other abdominal organs appeared normal. The gall bladder was shrunken and strongly embedded between the right and the quadrate lobes. The caudate and right lateral lobes were adherent to the diaphragm. Histologically, the liver parenchyma was essentially normal. Small foci of ectopic cells indicated that necrosis had occurred earlier, and the distribution was centrolobular.

Penicillin-Treated Dog 32.—No biochemical tests were carried out on this dog. It appeared, however, destined to survive the operation and was in good condition when killed on the fourth postoperative day.

On postmortem examination the liver showed areas of local necrosis on the left and right medial tips of the quadrate and caudate lobes (Fig. 5). The gall bladder was necrotic, but the other abdominal organs appeared normal. Histological examination showed an increase in the pericentral adventitia of many of the larger radicles of the hepatic vein, but it looked as though it were of long standing. There were blood cells in branches of the hepatic artery. Except for a few areas of local necrosis, the liver parenchyma was normal.

COMMENT

We have confirmed the observation of previous workers that ligation of all the branches of the hepatic artery in the dog is a fatal operation. Even though this experiment was initially designed with an entirely different purpose in view (which we failed to accomplish) we stumbled on the significant fact that one small dose of penicillin G potassium enables dogs to survive the loss of the hepatic artery. The work of W. S. Hoffman [9] and J. Ungar [10] has shown that the penicillin we used disappears from the plasma in three hours. Our observation indicates that when the bacterial population of anaerobes is reduced to a sublethal concentration, the defensive forces of the body can resist those that are left. Possibly this includes removal by phagocytosis of miliary necrotic areas in which they live. Fraser [1a] has described these, although we have not seen them.

What was puzzling about animals surviving the loss of the hepatic artery was that they continued in good health after the injections of penicillin were stopped. Several investigators maintain that this is the result of arterial revascularization [8g] during the week of treatment. Since our dogs almost uniformly survive after one dose, which lasts about three hours, this explanation is untenable. Moreover, Tanturi is at pains to point out that some of his penicillin-treated animals that survived did not show such regenerated collateral vessels.

9. Hoffman, W. S.: Subcutaneous Versus Intramuscular Administration of Penicillin, J. Lab. & Clin. Med. **31**:1165, 1946.

10. Ungar, J.: Penicillin in Tissue Exudates After Injection, Lancet **1**:56, 1950.

SUMMARY AND CONCLUSIONS

1. The hepatic artery was ligated in three dogs. No penicillin was given. All three died between 24 to 36 hours.

2. The hepatic artery was ligated in nine dogs. Each dog received 100,000 units of penicillin G potassium subcutaneously immediately after the operation. One died on the 7th postoperative day; in another distemper developed, and this dog was killed on the 13th day. The others survived until they were killed.

3. Biochemical tests indicated that some liver dysfunction developed in the penicillin-treated group, but liver function returned to normal within nine days postoperatively. This is in keeping with the histological observation that mild, transient, and sometimes localized necrosis occurred in some dogs and was followed by postnecrotic repair and regeneration.

4. Since dogs survive the loss of the hepatic artery when only one small dose of penicillin is given, their continued survival cannot be due to revascularization, since this is inconceivable in a matter of three hours.

Professor J. Markowitz gave valuable advice in completing this work.

Dr. W. S. Hartroft and members of his laboratory examined the histological specimens.

CANCER OF THE TONSIL

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CARCINOMA and lymphoma of the tonsil are more easily recognized than cured, and the ease with which a diagnosis of cancer in this area may be made is offset by the poor prognosis and poor results achieved in therapy. Although the average practitioner may have the opportunity to see only isolated examples of this condition during a lifetime of practice, its relative frequency is high when compared with the incidence of other cancers of the pharynx.

The present report is concerned with evaluation of a series of 162 patients with cancers of the tonsil seen in the outpatient clinic or admitted to the Pondville Hospital (Massachusetts Department of Public Health) from 1927 to 1945 inclusive. This hospital is a state institution for the treatment of malignant disease.

INCIDENCE

During the period encompassed by this report there were seen 162 patients with malignant tumors in the region of the tonsil. This number formed 1.2% of all patients with cancers. In a series reported from the Memorial Hospital in New York City, such tumors formed 2% of all cancers.[1] Schall [2] found them to occur once among every 106 cancer patients at the Huntington Memorial Hospital.

In most previously reported statistical analyses of pharyngeal lesions, cancer of the tonsil has been considered to be the second most common tumor of the pharynx, being second only to extrinsic cancer of the larynx in frequency. In this series tonsillar tumors formed 22.2% of all pharyngeal cancers.

SEX AND AGE INCIDENCE

Cancer of the tonsil is overwhelmingly a disease of males. Schall [2] reported an incidence of 88.7% in the male; Mattick,[3] 91.3%; Martin and Sugarbaker,[1] 86%; Despons,[4] 92%; Nathanson,[5] 95%; Burnam,[6] 77.5%.

From the Pondville Hospital (Massachusetts Department of Public Health), Walpole, Mass.

1. Martin, H. E., and Sugarbaker, E. L.: Cancer of the Tonsil, Am. J. Surg. **52**:155-196 (April) 1941.

2. Schall, L. A.: Carcinoma of the Tonsil: Statistical Study of 230 Cases, New England J. Med. **211**:997-1000 (Nov. 29) 1934.

3. Mattick, W. L.: The Diagnosis and Treatment of Cancer of the Tonsil, Radiology **35**:268-273 (Sept.) 1940.

4. Despons, J.: Cancer de l'amygdale, Rev. de laryng. **49**:305 (May 15); 339 (May 31) 1928.

5. Nathanson, E. A.: Cancer of the Tonsils, Arch. Clin. Cancer Res. **3**:181, 1927-1928.

6. Burnam, C. F.: Diagnosis and Treatment of Malignant Tonsil Conditions, Surg., Gynec. & Obst. **55**:633-639 (Nov.) 1932.

In the present series 139 of 141 carcinomas occurred in males, with an incidence of 98.6%. Curiously enough, this sex preponderance did not hold true for the lymphomas, of which 12 of 21 occurred in males. This divergence of incidence for the two diseases has not been adequately stressed in previous reports.

Malignant tumors of the tonsil occurred predominantly in the age group from 55 to 79 years, with a peak incidence at 65 to 69 years (Table 1). The extremes were a child 3 years old with a lymphosarcoma and a man 87 years of age with a carcinoma. The age distribution coincides roughly with that expected for cancer patients in general.

PATHOLOGIC TYPES

Carcinoma of the tonsil occurs predominantly as epidermoid carcinoma. Although tumors without evidence of keratinization and with a close resemblance to the

TABLE 1.—*Age Distribution*

Age, Yr.	Male	Female	Total
3	1	..	1
35-39	2	..	2
40-44	2	1	3
45-49	7	..	7
50-54	10	2	12
55-59	21	1	22
60-64	24	..	24
65-69	27	5	32
70-74	27	..	27
75-79	21	2	23
80-84	6	..	6
85-89	3	..	3

TABLE 2.—*Pathologic Types*

	Epidermoid Carcinoma				Undifferentiated Carcinoma	Lymphosarcoma	Hodgkin's Disease	Unclassified	Total
	Ungraded	I	II	III					
Right	5	10	31	14	0	6	0	6	72
Left	8	16	28	11	2	9	0	8	82
Bilateral	0	0	1	0	0	5	1	0	7

transitional type of epithelium occur not infrequently, it is not necessary to place them in a separate category as transitional types of carcinoma. In a study of a series of tonsillar carcinomas of increasingly higher degrees of malignancy, the transitional type can readily be seen as a nonkeratinizing form of epidermoid carcinoma. For this reason, and because of the possibility of confusion with other types of tumors derived from true transitional epithelium, the term has not been used.

The epidermoid carcinomas have been classified on the basis of three grades, depending primarily on mitotic activity and degree of differentiation of the tumor cells (Table 2). There were no examples in this series of the lymphoepithelioma of Regaud. Two examples of undifferentiated carcinoma occurred in which there was at first considerable difficulty in determining whether the tumor was of epithelial or connective-tissue origin.

In 13 cases the biopsy material was insufficient for accurate grading. In 14 cases no biopsy material was obtained to corroborate the clinical diagnosis. These occurred principally in the early years covered by the survey. The patients are included

in the series because they had lesions which were unequivocally primary malignant tumors of the tonsil. They will be treated in a separate category because the histologic classification is unknown.

The malignant tumors derived from the lymphoid tissue of the tonsil displayed the usual characteristics of lymphosarcoma. Although reticulum cell sarcoma and giant follicular lymphoma have been observed in the tonsil, there were none in this series. There was one case of Hodgkin's disease.

The follow-up system of the Pondville Hospital through the Department of Public Health takes in almost 98% of all patients with cancer. The follow-up of this group of patients with tonsillar cancer has been complete except for 1 patient, who was lost to the follow-up six months after a course of therapy. The patients have been studied in the outpatient clinic subsequent to therapy, or information as to the final outcome of the disease has been obtained from other sources. The one patient lost in follow-up will be excluded from the statistical study.

SYMPTOMS

Symptoms and signs observed in these patients are summarized in Table 3. In the majority of cases the lesion was advanced when first seen. The most common

TABLE 3.—*Most Frequent Presenting Symptoms*

	Cases
Mass in the neck	44
Sore throat	40
Pain and difficulty in swallowing	24
Pain in throat	12
Pain in ear	7
Soreness of mouth	5
Pain in side of head	4
Weight loss	4

symptom noted was a mass in the upper cervical region, occurring in a total of 44 patients. Sore throat, the next most common presenting symptom, occurred in 40 patients. Pain referred to the ear and radiating up to the head to the temporal or occipital areas was considered an ominous sign and usually indicated extensive local infiltration by tumor.

Weight loss was complained of by a large number of patients. However, no attempt was made to analyze this symptom on a quantitative basis. It was the presenting and only symptom in four cases.

The duration of symptoms in 143 patients from whom an accurate history was available averaged 5.2 months from the onset to the time of consultation at this clinic. Eighteen, or 12.6%, gave a history of duration of symptoms of four weeks or less.

CLINICAL CHARACTERISTICS

The clinical characteristics of carcinoma and lymphosarcoma are usually sufficiently distinctive to allow an accurate clinical diagnosis to be made.

Carcinoma of the tonsil occurs as a nodular, ulcerated lesion which may involve the anterior or posterior pillar or may appear to arise in the tonsillar fossa proper. Distinction of carcinoma of the pillars from that of the tonsil is frequently not possible owing to the advanced character of the lesion. A characteristic feature of this

ulcerated lesion is its induration. Even in the earlier stages, induration is prominent and can be felt by digital examination of the lesion with the gloved finger. In the late stages the neoplasm may extend laterally to be continuous with the mass of involved cervical lymph nodes. Occasionally the tumor is papillary or exophytic, with a minimum of ulceration and infiltration.

Extension of the carcinoma from the primary site occurs peripherally and involves contiguous structures. Anteriorly, the anterior pillar, buccal mucosa, alveolar ridge, and floor of the mouth may be the sites of extension. Superiorly, the carcinoma involves the supratonsillar fossa, soft palate, hard palate, and uvula. In an advanced lesion there may be extension beyond the midline on the soft and hard palates. Posteriorly, it involves the posterior pillar, lateral and posterior pharyngeal wall, and occasionally the nasopharyngeal wall. Inferiorly, extension of tumor occurs to the lateral portion of the tongue, base of the tongue, pyriform sinus, and pharyngeal wall, and it may involve the epiglottis.

The clinical picture of lymphoma of the tonsil varies distinctly from that of carcinoma. The tumor is usually globular, frequently with no ulceration or with only minor ulceration. The tumor may extend into the oropharynx as a polypoid type of lesion and may cause considerable mechanical difficulty in swallowing. Occasionally, the lesion assumes the appearance of a peritonsillar abscess, and repeated attempts may be made to incise the tumor. In 25% of this series the lesion involved both tonsillar areas, a feature which may aid in diagnosis.

Extension to the regional lymph nodes is an early and frequently seen accompaniment of all malignant tumors involving the pharynx. In this series, 44 patients reported as their first complaint a mass in the neck. In the series of Martin and Sugarbaker,[1] one-third of all patients noted enlarged cervical nodes as the initial symptom.

Adenopathy was present in 122, or 75.7%, of this series, whether initially or at some period during the course of the disease. Bilateral adenopathy was present in 18, or 11.2%, of all patients. The former figures are comparable to those of other series: Schall,[2] 92%; Mattick,[3] 77.3%; Martin and Sugarbaker,[1] 76%; Burnam,[6] 70.3%.

RESULTS OF THERAPY

Therapy of malignant disease of the tonsil has been adequately discussed in previous articles.[7] Suffice it to say that surgical procedures generally are considered to play no part in the therapeutic armamentarium. Surgical therapy of even relatively localized lesions results in a low incidence of clinical cures. In the case of advanced lesions, it is technically difficult, is deforming to the patient, and rarely results in cure. The present accepted methods of therapy include some type of radiotherapy: teleradiotherapy, external roentgen therapy, intraoral roentgen therapy, or interstitial radium or radon therapy, either to the primary or to metastatic lesions. Combinations of these modes of radiotherapy are more often used.

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In computing survival rates, the records of 161 patients were considered. It must be emphasized that this series is completely unselected and consists of all patients seen in the clinic, whether therapy was given or not. This basis for the consideration of survival rates conforms with the method adopted by the American

TABLE 4.*—*General Summary*

	No. of Cases
Total Experience: All patients applying	162
Sections A of Table: Patients not previously treated	123
Sections B of Table: Patients previously treated	38
Other (a) Applied after treatment elsewhere; no evidence of cancer on admission or thereafter	1
Other (b) Consultation only, no treatment requested	0

Epidermoid Carcinoma

Section A: Patients Not Previously Treated

Results at End of Five Years	No. of Cases: With Microscopic Proof	Without Microscopic Proof	Total
Group 1: (c) Refused proffered treatment	4	5	9
(d) Untraced for full 5 yr. without recurrence at last examination	1	..	1
Group 2: (e) Dead within 5 yr. of other causes without recurrence of cancer	5	1	6
Group 3: (f) Dead; cancer present or died of complications of treatment	80	4	84
Group 4: (k) Living; continuously free of cancer, verified by medical examination at 5 yr.	5	..	5

Section B: Patients Previously Treated

Group 1: (c) Refused proffered treatment	10	2	12
Group 3: (f) Dead; cancer present or died of complications of treatment	21	1	22
(j) Untraced full 5 yr. with cancer at last examination	1	..	1
Group 4: (k) Living; continuously free of cancer, verified by medical examination at 5 yr.	1	1	2

Lymphoma

Section A: Patients Not Previously Treated

Results at End of Five Years	No. of Cases: With Microscopic Proof	Without Microscopic Proof	Total
Group 1: (c) Refused proffered treatment	1	..	1
Group 2: (e) Dead within 5 yr. of other causes, without recurrence of cancer	1	..	1
Group 3: (f) Dead; cancer present, or died of complications of treatment	14	..	14
Group 4: (k) Living; continuously free of cancer, verified by medical examination at 5 yr.	3	..	3

Section B: Patients Previously Treated

Group 4: (k) Living; continuously free of cancer, verified by medical examination at 5 yr.	1	..	1

* This table uses an abridgment of the method recommended by the American College of Surgeons for the reporting of series of cancer cases.

College of Surgeons (Table 4). Use of three year survival rates was found to be unsatisfactory.

The over-all five-year survival rate for unselected patients seen between 1927 and 1945 was 7.2%. The five-year survival in the lymphosarcoma group was 22.2%, as contrasted with a rate for carcinoma of 5.0%. A similar gradient was noted for the average survival period following onset of treatment. For patients with lympho-

sarcoma this period was 20.6 months, in contrast to the maximum average survival period of 16.4 months for those with carcinoma.

There were 22 patients who were not treated or who received less than 1,000 r (by air) of radiation. Excluding these from the statistical analysis gives a five-year survival rate of 8.5%. Considering only a group of 60 patients receiving an equivalent of 5,000 r (by air) or more of therapy, an amount which may be considered the minimum for adequate treatment, yields a five-year survival rate of 12.3%.

EFFECT OF ADENOPATHY ON SURVIVAL

The occurrence of metastases to cervical lymph nodes is an important factor in determination of the outcome of the disease. In the absence of clinical evidence of cervical nodal metastases, the five-year survival rate was 20%. In the presence of unilateral adenopathy, the five-year survival decreased to 4%. In the presence of bilateral lymph nodal involvement, the five-year survival fell to zero.

The importance of cervical metastases is similarly illustrated by correlation with the average survival period. In patients without clinical evidence of cervical metastasis, the mean survival period following onset of therapy was 20.9 months. With

TABLE 5.—*Relation of Duration of Symptoms to Survival Rates*

	2 Mo. or Less	2-6 Mo.	More Than 6 Mo.
Carcinoma			
No. of cases	40	50	39
5-yr. survival rate	13.9	4.2	0
Lymphosarcoma			
No. of cases	9	8	3
5-yr. survival rate	33.3	14.3	0

unilateral adenopathy, the mean survival was 12.7 months. With bilateral adenopathy, the survival period was reduced to 7.9 months.

For the patients with lymphosarcomas, the mean survival period would be increased if those with generalized lymphosarcomatosis were excluded. Thus, in three patients the disease was generalized at the time of initial examination, and in one patient generalization of the involvement developed shortly after the onset of therapy. Survival periods for these patients were 1, 2, 4, and 27 months after onset of therapy, respectively. Of the patients with no adenopathy, one lived less than 18 months, one lived less than 60 months, and two survived more than 60 months without disease. In the presence of unilateral adenopathy, 27.2% died in less than 6 months, 55.6% died in less than 12 months, and 63.6% died in less than 18 months. In the presence of bilateral adenopathy, all patients died in less than six months.

PREVIOUS THERAPY

Of the patients seen, 38 had received previous therapy of various types at other institutions, and 1 had received previous therapy but was free of disease at the time of consultation at the clinic. Fifteen patients had received roentgen therapy and appeared with recurrences. There were no five-year survivals in this group. Two patients had been treated by interstitial application of radon seeds, with no five-year survivals. Among five who had had surgical therapy of some type, there was one

five-year survival. Routine tonsillectomy on this patient revealed an unsuspected lymphosarcoma. He was treated with external radiation at this institution. He died of unrelated causes eight years later, at which time there had been no recurrence.

Eight patients had received previous roentgen therapy plus radium therapy. Among these there was one five-year survival. This patient received further x-ray treatment here and was free of disease 17 years later. Five patients received a combination of surgical therapy and roentgen therapy, with no survivors.

Among the 39 previously treated patients, the result was indeterminate in one, who died of asphyxiation 45 months after therapy. Two patients lived five years or longer without disease, a five-year survival rate of 5.9%.

CLINICAL CLASSIFICATION OF CARCINOMA OF THE TONSIL

It would be desirable for purposes of prognosis and for more accurate comparison of various series to attempt a division of carcinoma of the tonsil into stages, as is done with tumors at other locations. Accordingly, an arbitrary classification related to the clinical extent of the disease was set up (Table 6).

Stage I.—Small localized tumors either in situ or localized to a small area of the tonsil or pillars. No adenopathy.

TABLE 6.—*Survival in Carcinoma of the Tonsil with Reference to Stages*

	I	IIa	IIb	IIIa	IIIb	IV
Cases	0	12	8	13	58	23
5-yr. survival, %	..	33.3	25	15.4	0	0
Average survival period, mo.	..	27.8	21.1	14.9	11.1	9.1

Stage II.—Localized tumors with or without extension to the anterior or posterior pillar but without extension to other contiguous structures. The lesion measures less than 4 cm. in diameter.

(*a*) No adenopathy.

(*b*) Ipsilateral adenopathy.

Stage III.—Tumors with extension to the buccal mucosa, base of the tongue, soft palate, uvula, hard palate, or lateral pharyngeal wall. The primary lesion measures more than 4 cm. in diameter. Adenopathy is usually present but may be absent.

(*a*) No adenopathy.

(*b*) Ipsilateral adenopathy.

Stage IV.—Tumors with extensive involvement of the pharynx and oral cavity, massive adenopathy, bilateral adenopathy, or distant metastases.

So far as possible, the cases were regrouped to conform with this classification. In some cases, the clinical descriptions were not sufficiently detailed to justify a reasonably accurate grouping, and these were eliminated. Computation of five-year survival rates and average post-therapy survival periods suggests some value to this procedure, although the number of cases in each category is rather small for sound statistical deduction.

AUTOPSY MATERIAL

Of the series, 31 patients eventually came to autopsy. Of these patients, there were two in whom residual tumor was not found. In both cases the diagnosis had been previously verified by biopsy. One patient died of cardiac amyloidosis, hyper-

trophy and dilatation of the heart, and anasarca. The second patient died of arteriolonephrosclerosis, hypertrophy and dilatation of the heart, and anasarca.

There were two cases of lymphosarcoma with generalization of the disease. In one additional case the disease was limited to the tonsillar region and to the cervical lymph nodes.

In one case of undifferentiated carcinoma, autopsy revealed metastases to cervical lymph nodes, pleura, ribs, heart, mesenteric and paravertebral lymph nodes, and small bowel.

In 20 cases of epidermoid carcinoma, autopsy failed to reveal metastatic involvement beyond that in the cervical lymph nodes. In five cases there were, in addition to extension to the cervical nodes, metastases to distant organs. Thus in 6 of 26 cases, or 23.1% of the cases of carcinoma of the tonsil in which autopsy was done, there were metastases below the level of the cervical lymph nodes.

COMMENT

Although the tonsils and oropharynx are accessible and are easily visualized, the diagnosis of cancer of the tonsil is made in the late stage of the disease in a large number of cases. The early stages are completely or almost completely asymptomatic, and pain or sore throat does not occur until extension to contiguous structures or extensive infiltration or ulceration has occurred. The most common presenting symptom, mass in the neck, is in itself a manifestation of advanced carcinoma and is of grave prognostic significance. The presence of bilateral adenopathy indicates a hopeless prognosis.

Effectiveness of therapy is dependent to a considerable extent upon the pathologic type of tumor present. Well-differentiated, keratinizing epidermoid carcinomas, although usually considered as of low malignancy and slow growth, had post-therapy survival periods significantly lower than those of poorly differentiated carcinomas. The explanation for this phenomenon lies in the relative radioresistance of the well-differentiated tumors and the greater radioresponsiveness of the poorly differentiated tumors. For the same reason, the lymphosarcoma, ordinarily considered a highly malignant tumor with rapid dissemination and growth, had the best post-therapy survival period and five year survival rate provided extension beyond the cervical lymph nodes had not occurred.

SUMMARY

Cancer of the tonsil formed 1.18% of all malignant diseases as seen in a hospital devoted exclusively to the treatment of cancer. Among the pharyngeal tumors, it was second in frequency only to extrinsic carcinoma of the larynx, forming 22.2% of pharyngeal cancers. In the series of 141 carcinomas and 21 lymphomas of the tonsil, carcinoma occurred in the male in 98.6% of cases; lymphosarcoma occurred with approximately equal frequency in the male and female. Both types occurred with greatest frequency in the age group from 55 to 79, with a peak incidence at 65 to 69 years. Lymphosarcoma occurred in both tonsillar areas in 25% of cases.

The presenting symptoms in order of frequency were: mass in the neck, sore throat, pain and difficulty in swallowing, and pain in the throat. Weight loss was a common accompaniment and in four cases was the presenting and only symptom.

Adenopathy occurred in 75.7% of patients; 11.2% of all patients displayed bilateral adenopathy.

The over-all five-year survival rate in an unselected series of 161 patients was 7.2%. The presence of ipsilateral and bilateral metastases to cervical lymph nodes decreased the five-year survival rate from 20% to 4% and zero, respectively, and decreased the survival period from 20.9 months to 12.7 months and 7.9 months, respectively. The five-year survival rate for patients previously treated elsewhere was 5.9%.

Exclusion from the total series of patients receiving less than 1,000 r of therapy increased the five-year survival rate to 8.5%. For patients receiving 5,000 r or more of therapy, the five-year survival rate was 12.3%.

Classification of tonsillar carcinoma into stages depending on the extent of the lesion is of importance in prognosis and will allow more accurate comparison of various series of results of therapy.

In a series of 31 autopsies, two patients revealed no evidence of recurrent tumor. Six of 26 patients, or 23.1% of those with residual carcinoma, revealed metastases elsewhere than in the cervical nodes. Of the lymphosarcomas, two were generalized and one was localized to the tonsil and cervical nodes.

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EXPERIMENTAL RENAL TRANSPLANTATION: I. EFFECT OF NITROGEN MUSTARD, CORTISONE, AND SPLENECTOMY

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ON THE basis of existing evidence the cause for failure of renal transplantation is due to the host developing antibodies in response to the foreign protein of the graft. This immune process is not only a natural phenomenon but also a valuable protective biological reaction. The present paper is concerned with methods of modifying or depressing this renal antigen-antibody response by use of nitrogen mustard (methyl bis [β-chloroethyl] amine hydrochloride), cortisone, and splenectomy. Philips, Hopkins, and Freeman,[1] and others [2] have demonstrated that nitrogen mustard will suppress development of antibodies. Germuth and co-workers [3] have shown that cortisone is effective for states of hypersensitivity. Rich and co-workers [4] have indicated also that cortisone inhibits antigen-antibody reactions. Persky and Jacob,[5] however, failed to note any increased survival of renal transplantation in the cortisone-treated dog. The role of the spleen in the development of antibodies has been explored. After intravenous injections of antigens, high antibody titers were demonstrated in the splenic extracts of the dogs.[6] In splenectomized animals the ability to produce precipitating antibodies is reduced, and these animals are also less responsive to small injections of antigen than animals which have not been operated on.[7]

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PROCEDURE

Healthy adult male and female dogs were used in the experiment. All operations were performed with use of intravenous injections of secobarbital (seconal®) sodium anesthesia, and the usual aseptic precautions were observed. A donor kidney obtained from an untreated dog was perfused with heparin-saline solution. Homotropic transplantation was performed by suture anastomosis of the vascular pedicle of the donor kidney directly to the renal vessels of the heparinized host. The maximum time needed to perform arterial anastomosis was 30 minutes. Prior to suturing the renal vein, the arterial clamp was released for a short time and blood was permitted to wash through the kidney. After venous anastomosis, a polyethylene catheter was placed in the ureter and brought out through one end of the abdominal wound. In the present experiment four dogs were given 0.5 mg. of nitrogen mustard per kilogram until leucopenia indicated depression of the hematopoietic system. There was an average of 80% inhibition of polymorphonuclear cells. Six other dogs were treated with nitrogen mustard and given a divided daily intramuscular injection of 50 mg. of cortisone.[8] In four additional dogs splenectomy was employed as well as nitrogen mustard and cortisone.

RESULTS

It has been determined elsewhere [9] and in this experiment that after homoplastic renal transplantation in control dogs there is renal function for about one to five

Duration of Renal Function Following Transplantation

No. of Dogs	Therapy	Range, Days	Mean, Days
5	None (control dogs)	1-5	3 ± 1.0
4	Nitrogen mustard	1-8	4.5 ± 2.7
6	Cortisone and nitrogen mustard	4-20	13.5 ± 5.2
4	Cortisone, nitrogen mustard, and splenectomy	5-20	16.2 ± 3.3

days, with an average of approximately three days. Renal transplantation in dogs treated with nitrogen mustard resulted in kidneys that functioned for an average of four days. Nitrogen mustard and cortisone used in combination prolonged renal function from 4 to 20 days, with an average of 14 days. Nitrogen mustard, cortisone, and splenectomy did not produce any significant increase in duration of renal function other than that observed with nitrogen mustard and cortisone. These results are expressed in greater detail in the accompanying Table.

Immediately upon cessation of renal function, the kidneys of the dogs were excised and sectioned. All kidneys were enlarged, soft, and edematous. The rejection by the host of the transplanted kidney assumes the form of mobilization and infiltration of lymphocytes, particularly about the glomeruli (Fig. 1). No significant qualitative difference in the renal microscopic pattern was observed in all dogs studied.

COMMENT

Since renal transplantation is essentially an all-or-none operation, this experiment was unsuccessful. Regardless of the agent or combination of agents employed to inhibit antibody production, the transplanted kidneys did not persist permanently in function and vitality. As determined by standard statistical tests, an apparently

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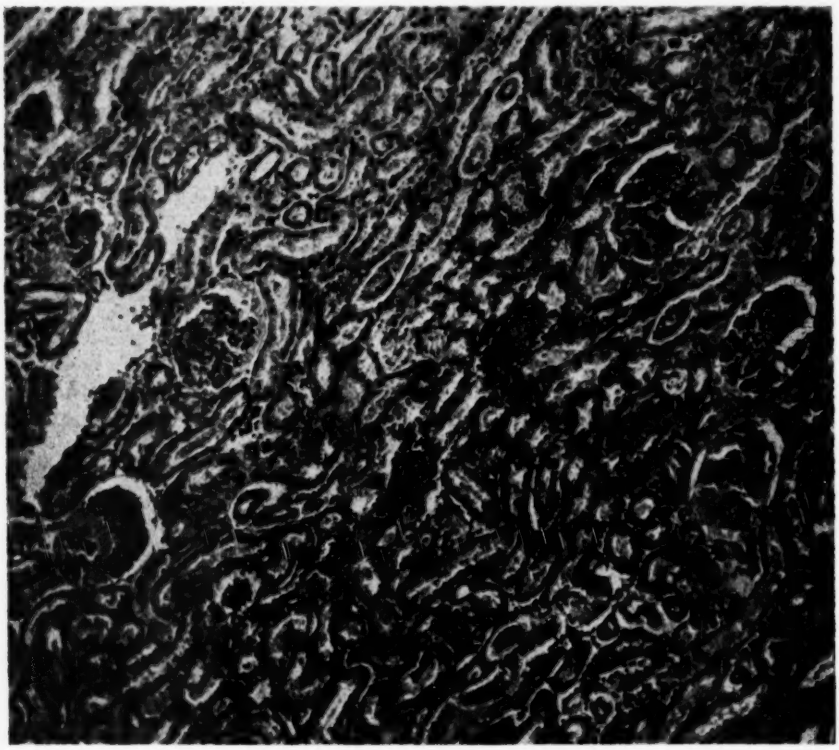
significant prolongation of renal function has been demonstrated in homotropic, homoplastic transplanted kidneys by use of nitrogen mustard and cortisone. The same effect was produced by splenectomy, nitrogen mustard, and cortisone. Although the number of dogs studied in each group is small, certain data would indicate that the differences noted in function time between control and experimental animals are significant. After homotropic, homoplastic renal transplantation in the untreated dog, other investigators have observed that the kidney usually does not function longer than five days. Our experience confirms this observation. In



Photomicrograph of dog kidney that functioned eight days following transplantation to a dog treated with nitrogen mustard, cortisone, and splenectomy. Observe lymphocytic infiltration. × 135.

the present experiment 3 dogs treated with cortisone and nitrogen mustard, and 3 dogs treated with cortisone, nitrogen mustard, and splenectomy had functioning kidneys 14 to 20 days following transplantation.

Certain additional variables must be considered which may modify the significance of the results observed. Those dogs that had longest survival of renal function also showed greatest depression of the hematopoietic system. In addition, the nitrogen mustard produced anorexia and considerable subsequent loss of

weight in the postoperative period in these animals. In 1927 Marpurgo [10] indicated a relationship between the take of a graft and the nutritional status. Depressed metabolism and inadequate nutrition may be associated with the greater survival time of transplanted tissues. It is possible that the increased time of renal function observed in the present investigation is related to the poor nutritional status of the treated dogs. Additional experiments are under way to investigate this aspect of the problem.

SUMMARY AND CONCLUSIONS

Nitrogen mustard, cortisone, and splenectomy have been shown to prolong the take of homotropic, homoplastic renal transplantation in dogs. The possibility has been discussed that this effect may be the result of the impaired nutritional status of the treated dog. The increased duration of function observed may be significant, however, and warrants further study.

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EFFECTS OF DEXTRAN AND OF POLYVINYLPYRROLIDONE ADMINISTRATION ON LIVER FUNCTION IN MAN

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THE USE of polyvinylpyrrolidone (PVP)[1] and of dextran [2] has been proposed for increasing the volume of plasma after hemorrhage and for the treatment of shock. Earlier experience with acacia used for this purpose indicated that it impaired liver function.[3] In addition, the use of acacia depressed the formation of plasma protein,[4] possibly because of its action on the liver. Although dextran and polyvinylpyrrolidone have been used extensively in foreign clinics, there is little specific information concerning possible ill effects on the liver function of man. Bohmansson and co-workers have made some studies of dextran, using for this purpose bile pigment, hippuric acid, and phosphatase determinations. We have extended these studies by means of other liver function tests, including several generally considered to be more sensitive than those used by these workers, and, in addition, have made similar studies of polyvinylpyrrolidone.

This work was done under contract between the Department of the Army and the University of Pennsylvania.

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METHOD

The patients studied were those in the general surgical wards. Most of them were studied during the postoperative period after a variety of major and minor procedures.

Blood specimens were collected the day before infusion of the plasma expander, and a 24-hour collection of urine was made. The dextran or polyvinylpyrrolidone [5] was given by vein in 1-liter amounts at a rate of 3 to 16 ml. per minute. Certain patients were given a second 1-liter infusion on the following day. Urine was again collected during the 24-hour period immediately after the infusion. A second specimen of blood was collected on the first or second day after the infusion and a third set of specimens seven to nine days after the infusion. The patients were asked to return after one month, when the tests were again repeated. A few patients were studied for as long as six months.

Patients receiving 6 liters of dextran were given 1-liter infusions daily for six days. Specimens were obtained before and after the first liter and again 10 days later, 4 days after the last infusion.

The need for repetition of the liver function tests three times within a week limited the number and the complexity of procedures that could be applied. The studies selected included measurement of serum total bilirubin concentration by the method of Malloy and Evelyn,[6] with a reading of the direct-reacting fraction at one minute according to Ducci and Watson.[7] Retention was measured 45 minutes after the injection of 5 mg. of sulfobromophthalein sodium per kilogram of ideal body weight. Its concentration in plasma was determined photometrically. Corrections were applied for hemolysis, turbidity, and bilirubin according to a method developed in this laboratory.[8] Thymol turbidity [9] and zinc turbidity [10] were measured by use of a photoelectric photometer. Thymol reagents were prepared according to de la Huerga and Popper [11] and adjusted to pH 7.55 and pH 7.80. Thymol flocculation was recorded, if present, 18 hours after setting up the test. The cephalin-cholesterol-flocculation test [12] was done with precautions, described in an earlier report from this laboratory,[13] with use of difco* reagent. Lipid turbidity determinations [10] were included to aid in the detection of hyperlipemia, which might result from involvement of the biliary tract, and, also, to aid in the evaluation of changes in

5. Nine patients received 1 liter of a preparation of polyvinylpyrrolidone manufactured in Germany and bottled by the Schenley Laboratories, Inc. The intrinsic viscosity of the material was 0.245, the average molecular weight approximately 30,000. The remainder of the patients received polyvinylpyrrolidone manufactured by the General Aniline and Film Corporation. The average molecular weight of this material was 33,000; the K value was 33. Both preparations contained 3.5% of polyvinylpyrrolidone in 0.85% sodium chloride solution.

Dextran was supplied by the Commercial Solvents Corporation. It was given as a 5.9% solution. The results of a typical analysis were as follows: viscosity 3.18 centipoises; no precipitation at 45% methyl alcohol; 88% precipitation at 58% methyl alcohol, and 12% precipitation at 80% methyl alcohol.

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thymol turbidity.[14] The serum protein was determined by means of the biuret reagent of Weichselbaum,[15] 27.8% sodium sulfate being used for the separation of the protein fractions.[16] The urobilinogen in the urine was estimated by the method of Watson, Schwartz, Sborov, and Bertie,[17] and the coproporphyrin excretion by the method of Watson and Schwartz.[18] The completeness of the urine collection was evaluated by creatinine determinations by the method of Bonsnes and Taussky.[19] The urobilinogen and coproporphyrin excretions were corrected by selecting the most plausible of the three creatinine values and adjusting the urobilinogen and coproporphyrin values by the ratio of plausible creatinine to found creatinine.

The use of surgical operations and of anesthesia may affect liver functions, as measured by the test we have used.[20] We have therefore studied a control group consisting of 15 patients similar to those who were given dextran or polyvinylpyrrolidone. The control patients did not receive blood or plasma transfusions, but most of them received the saline and dextrose infusions

TABLE 1.—*Averages*

Groups	Period	Bilirubin, Mg./100 Ml.		Thymol Turbidity Units		Zinc Turbidity Units	Phenol Turbidity Units	Protein, Gm./100 Ml.			Sulfobromophthalein Retention, %
		1st	Total	pH 7.55	pH 7.8			Total	Albumin	Globulin	
Control											
(15)	1st day	0.14	0.61	1.2	0.7	3.6	19.5	6.9	3.3	3.6	19.2
	2-3 days	0.16	0.49	1.2	0.8	3.6	17.5	6.9	3.2	3.7	14.6
	1 wk.	0.11	0.39	1.2	0.8	4.0	17.6	7.0	3.2	3.8	11.7
(15)	Follow-up	0.08	0.40	2.6	1.6	5.7	29.3	7.6	3.9	3.7	4.9
Polyvinylpyrrolidone, 1 liter											
(10)	Preinfusion	0.10	0.33	1.4	1.0	2.9	17.5	6.8	3.3	3.5	4.1
	1-2 days	0.08	0.38	2.1	1.6	2.6	53.3	6.1	3.1	3.0	6.0
	1 wk.	0.06	0.32	1.6	1.2	2.6	29.2	6.4	3.4	3.0	6.1
(9)	Follow-up	0.07	0.25	1.6	1.3	2.8	24.4	6.9	3.8	3.1	3.5
Polyvinylpyrrolidone, 2 liters											
(5)	Preinfusion	0.16	0.66	1.0	0.5	3.3	21.1	7.3	3.4	3.9	2.7
	1-2 days	0.12	0.55	1.9	1.3	2.5	59.7	6.3	3.2	3.1	7.2
	1 wk.	0.09	0.43	1.3	1.0	2.8	37.9	6.6	3.4	3.2	5.2
(3)	Follow-up	0.06	0.35	2.7	1.5	2.9	29.4	7.0	3.7	3.3	....
Dextran, 1 liter											
(10)	Preinfusion	0.20	0.84	0.8	0.5	3.1	18.2	6.6	3.1	3.5	10.2
	1-2 days	0.16	0.74	0.5	0.4	2.8	14.5	5.5	2.6	2.9	9.4
	1 wk.	0.15	0.50	0.7	0.6	3.7	15.0	6.5	3.0	3.5	6.4
(6)	Follow-up	0.08	0.45	1.3	1.1	3.5	31.6	7.2	4.0	3.2	3.4
Dextran, 2 liters											
(5)	Preinfusion	0.11	0.54	1.6	1.0	3.8	21.4	7.0	4.2	2.8	5.3
	1-2 days	0.13	0.45	0.7	0.5	2.4	10.3	5.3	3.2	2.1	4.5
	1 wk.	0.14	0.39	0.9	0.6	2.8	14.2	6.8	3.7	3.1	9.7
(5)	Follow-up	0.11	0.62	1.8	1.2	4.3	19.4	7.3	3.8	3.5	6.9
Dextran, 6 liters											
(8)	Preinfusion	0.31	0.84	1.2	0.8	3.9	15.3	6.5	2.7	3.8	....
	1-2 days	0.16	0.50	1.1	0.8	3.9	8.7	5.5	2.3	3.2	....
	10 days	0.15	0.62	1.3	1.0	3.9	9.5	5.6	2.3	3.3	....
(8)	Follow-up	0.12	0.39	1.1	0.7	3.9	18.3	7.0	3.3	3.4	....

14. von Frijtag Drabbe, C. A. J., and Reinhold, J. G.: Determination of Polyvinylpyrrolidone in Body Fluids by Means of a Turbidity Producing Reaction with Phenol, to be published.

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20. Zamchek, N.; Chalmers, T. C., and Davidson, C. S.: Pathologic and Functional Changes in the Liver Following Upper Abdominal Operations, Am. J. Med. **7**:409, 1949.

customarily given postoperative patients. A comparison of the mean values for the several groups (Table 1) shows that the control group compared well with the experimental groups, except for appreciably higher mean sulfobromophthalein retention.

Two patients were tested repeatedly during the follow-up period, and therefore the likelihood of detecting changes was greater than in the control subjects. In order to eliminate bias, only the results of a single series of tests done during the same period as the control group follow-up studies were included in the Tables.

The standard deviations (Table 2) were calculated from studies made of a group of 65 to 125 healthy young men and women.[21]

TABLE 2.—*Tabulation of Frequencies*

	Bilirubin, Mg./100 Ml.		Turbidity Tests, Units				Protein, Gm/100 Ml.			Sulfobromophthalein Retention, %
			Thymol							
	1st	Total	7.55	7.8	Zinc	Phenol	Total	Albumin	Globulin	
2 × S.D.	0.12	0.50	1.0	0.9	2.5	13.0	1.0	0.42	1.04	3.1
Control Subjects										
1-2 days										
Decrease	1	1	0	0	0	1	0	0	0	4
No change	12	13	14	14	15	14	15	15	15	9
Increase	1	0	1	1	0	0	0	0	0	1
1 week										
Decrease	1	2	1	1	0	2	1	1	0	7
No change	12	12	12	12	14	12	12	13	13	4
Increase	1	0	2	1	0	0	1	0	1	2
Follow-up										
Decrease	2	1	0	0	0	2	0	1	0	6
No change	10	12	5	11	10	5	8	4	13	3
Increase	1	0	8	3	3	6	5	8	0	0
Patients Receiving Dextran (6 Liters)										
1-2 days										
Decrease	2	2	0	0	0	1	5	2	1	..
No change	6	6	8	8	8	7	3	6	7	..
Increase	0	0	0	0	0	0	0	0	0	..
10 days										
Decrease	2	2	1	0	0	1	4	4	1	..
No change	6	5	6	8	8	7	4	4	7	..
Increase	0	1	1	0	0	0	0	0	0	..
Follow-up										
Decrease	2	1	0	0	0	0	0	1	0	..
No change	1	2	2	3	2	3	2	1	3	..
Increase	0	0	1	0	1	0	1	1	0	..

RESULTS

Table 1 shows the mean values of the control group and of the groups receiving polyvinylpyrrolidone in 1- and 2-liter infusions and dextran in 1-, 2-, and 6-liter infusions.

Effects of 1 Liter of Dextran.—Ten patients were studied. An increase in bilirubin occurred in one patient. This was offset by values decreasing from abnormal to normal in two others. Similar significant increases in sulfobromophthalein retention in two patients contrasted with significant decreases in four others. In four patients, cephalin-cholesterol flocculation was weakly positive when tested seven days after the infusion; in two there was a change in the opposite direction. One patient showed a marked increase in urobilinogen excretion (Table 5).

21. Neefe, J. R.; Kurtz, C. H.; Smith, H. D.; Reynolds, H. M.; Gambescia, J. M., and Reinhold, J. G.: Technique Book of the Hospital of the University of Pennsylvania, Philadelphia, University of Pennsylvania Press, 1951.

TABLE 3.—*Tabulation of Frequencies for Patients Receiving Dextran*

	Bilirubin, Mg./100 Ml.		Turbidity Tests, Units				Protein, Gm/100 Ml.			Sulfobromophthalein Retention, %
			Thymol							
	1st	Total	7.55	7.8	Zinc	Phenol	Total	Albumin	Globulin	
Dextran (1 Liter)										
1-2 days										
Decrease	1	1	0	0	0	0	6	4	0	4
No change	9	8	10	10	10	10	4	6	10	4
Increase	0	1	0	0	0	0	0	0	0	2
1 week										
Decrease	1	3	0	0	0	0	1	4	0	5
No change	9	7	10	10	10	10	9	6	9	5
Increase	0	0	0	0	0	0	0	0	1	0
Follow-up										
Decrease	1	3	0	0	0	1	0	0	0	2
No change	5	3	5	5	4	3	5	3	6	1
Increase	0	0	1	1	2	2	1	3	0	1
Dextran (2 Liters)										
1-2 days										
Decrease	0	0	2	1	1	2	4	4	1	1
No change	5	5	3	4	4	3	1	1	4	3
Increase	0	0	0	0	0	0	0	0	0	0
1 week										
Decrease	0	1	1	1	1	0	1	3	0	0
No change	4	4	4	4	4	5	4	2	5	3
Increase	1	0	0	0	0	0	0	0	0	2
Follow-up										
Decrease	0	1	0	0	0	1	0	3	0	1
No change	4	4	4	5	5	4	4	1	4	3
Increase	1	0	1	0	0	0	1	1	1	1

TABLE 4.—*Tabulation of Frequencies for Patients Receiving Polyvinylpyrrolidone*

	Bilirubin, Mg./100 Ml.		Turbidity Tests, Units				Protein, Gm/100 Ml.			Sulfobromophthalein Retention, %
			Thymol							
	1st	Total	7.55	7.8	Zinc	Phenol	Total	Albumin	Globulin	
Polyvinylpyrrolidone (1 Liter)										
1-2 days										
Decrease	1	0	0	0	0	0	2	4	0	1
No change	9	10	8	7	10	0	7	5	9	7
Increase	0	0	2	3	0	10	0	0	0	1
1 week										
Decrease	1	0	0	0	0	0	1	2	0	0
No change	9	10	10	9	10	5	8	7	9	6
Increase	0	0	0	1	0	5	0	0	0	3
Follow-up										
Decrease	1	0	1	1	0	1	0	1	0	0
No change	7	8	6	7	9	4	8	3	8	5
Increase	0	0	2	1	0	4	0	4	0	0
Polyvinylpyrrolidone (2 Liters)										
1-2 days										
Decrease	0	1	0	0	0	0	3	2	0	0
No change	4	4	3	3	5	0	2	3	5	2
Increase	1	0	2	2	0	5	0	0	0	1
1 week										
Decrease	1	1	0	0	0	0	2	0	1	0
No change	4	4	4	4	5	3	3	4	4	2
Increase	0	0	1	1	0	2	0	1	0	1
Follow-up										
Decrease	1	0	0	0	0	0	0	0	1	..
No change	2	3	1	1	3	2	3	2	2	..
Increase	0	0	2	2	0	1	0	1	0	..

Effects of 2 Liters of Dextran.—Five patients were studied. The retention of sulfobromophthalein occurred in two after the infusion and persisted in one four weeks later. In one of these patients the cephalin-cholesterol flocculation also became positive. In addition, both also showed increased urobilinogen excretions following administration of the second liter of dextran. Operation and anesthesia may have contributed to these findings, but the persistent sulfobromophthalein retention shown by one could not be explained on this basis. Thus there is a suspicion that dextran had some deleterious effect in this patient.

Effects of 6 Liters of Dextran.—Eight patients were studied by Dr. A. Mitchie. A change from negative to positive cephalin-cholesterol flocculation occurred in two. One showed a transient, weakly positive thymol flocculation and another a slightly elevated serum bilirubin concentration. Three patients returned for follow-up studies. In one, who returned after about five months, the liver function test showed normal findings except for a rise in zinc turbidity, which increased three units over the initial value of five units. In another patient the findings were normal for all liver

TABLE 5.—*Average Values for Urinary Urobilinogen and Coproporphyrin*

Group	Period	No. of Patients	Urobilinogen Excreted in Urine, Mg./24 Hr.	Coproporphyrin, γ/24 Hr.
Control	First day	8	4.5	136
	2d-3d day	8	4.1	159
	1 week	8	3.8	145
Polyvinylpyrrolidone, 2 liters	Preinfusion	4	8.1	163
	1-2 days	4	6.3	155
	1 week	2	4.9	87
Dextran, 1 liter	Preinfusion	3	9.0	211
	1-2 days	4	14.5	204
	1 week	1	...	...
Dextran, 2 liters	Preinfusion	5	3.1	125
	1-2 days	4	4.1	107
	1 week	2	3.5	137

function tests after three months. The third patient was tested twice. After three months this patient, who had shown a significant rise in thymol turbidity and flocculation three days after the last infusion, showed positive cephalin-cholesterol flocculation. When the patient was retested four months later, the results of all liver function tests had become normal.

Effects of 1 Liter of Polyvinylpyrrolidone.—Ten patients were studied. The only individual changes requiring comment were in sulfobromophthalein retention, which rose from 5.1% before to 10.2% after the infusion in one patient and from 10.6 to 28% in another. The first patient also showed a minor increase in urobilinogen excretion. The results of further tests on these patients, made after three months and one month, respectively, showed a return to the preinfusion values.

Effects of 2 Liters of Polyvinylpyrrolidone.—Five patients were studied. Sulfobromophthalein retention rose to 21% in one patient after the infusion and was still elevated at 8.8% four days later. Two months later the thymol and zinc turbidities had become abnormal. Unfortunately, the sulfobromophthalein retention test could not be done at this time. A diagnosis of neoplastic growth involving the sigmoid was made. It is probable that this patient's illness and the effects of the operation contributed to produce these abnormalities.

Follow-up Studies.—Comments on individual patients have been made in connection with a review of the effects of the different expanders. Although occasional abnormalities were encountered in the follow-up studies, in no instance did the frequency differ significantly from that in the control group. A comparison of the trend of the tests, as shown by the means of the successive periods, likewise failed to demonstrate any difference between the test groups and the control groups.

Only one reaction was noted that was possibly due to the injected material. This occurred in a woman who was to receive 1 liter of polyvinylpyrrolidone; after about 75 ml. had been injected, she complained of tightness in the chest and difficulty in breathing. The infusion was stopped, and she recovered rapidly without apparent ill effect. None of the other patients showed clinically any immediate or late symptoms or signs of toxicity.

COMMENT

No systematic study has been made, to our knowledge, of liver function tests to establish which of the large number described would most efficiently detect toxic effects on the liver of substances of the type being investigated. Experience with the study of liver disease has shown that groups of tests are more dependable than a single test. The group of tests used in the present study was found to be capable of detecting significant involvement of the liver in a high proportion of patients suffering from hepatitis and cirrhosis.[22] The limitations imposed by the necessity for frequent repetition of the tests, as previously mentioned, largely determined the final selection of the procedures used.

The effects of polyvinylpyrrolidone and dextran were evaluated according to the frequency with which significant changes appeared in the patients who had received infusions as compared with those in the control group (Tables 2, 3, and 4). A significant change was defined as two standard deviations from the preinfusion value of the polyvinylpyrrolidone or dextran groups, or the first value in the control group. The chi-square method was used to test the significance of the frequency with which these changes occurred. Corrections were made for small sample size according to Yates.[23] P values of 5% or less were considered significant.

The frequency with which significant changes occurred in serum bilirubin concentration, cephalin-cholesterol flocculation, zinc sulfate turbidity, sulfobromophthalein retention, serum globulin, thymol turbidity and flocculation, urobilinogen, and coproporphyrin did not differ to a significant degree from that in the control group.

The only changes observed in the groups receiving the plasma expanders that differed significantly from the controls were the decreased serum total protein and albumin concentrations one day after the infusions. These may be attributed to hemodilution brought about by addition of a considerable amount of oncotically active material. Table 1 shows that after seven days the preinfusion values had been largely regained in the groups receiving 1- and 2-liter infusions of dextran but not in the groups given polyvinylpyrrolidone, which required a longer time.

22. Neefe, J. R. ,and Reinhold, J. G.: Laboratory Aids in the Diagnosis and Management of Infectious (Epidemic) Hepatitis, Gastroenterology **7**:393-413, 1946; Studies of Responses of Certain Hepatic Tests in Diseases of the Liver and Biliary Tract, ibid. **9**:656-671, 1947.

23. Fisher, R. A.: Statistical Methods for Research Workers, Ed. 6, London, Oliver and Boyd, Ltd., 1936.

The cause of the increase in thymol and phenol turbidity following the administration of polyvinylpyrrolidone has been explained elsewhere.[14]

The absence of definite evidence of liver damage following 1-liter infusions of dextran or polyvinylpyrrolidone led us to increase the amounts administered. Five patients therefore were given 2 liters, 1 liter on each of two successive days. The larger amounts also failed to cause significant differences in the patients treated with polyvinylpyrrolidone. Some moderate changes occurred in two patients after the infusion of 2 liters of dextran, and these persisted in the follow-up period. Similar changes were encountered in control patients, and the probability of the changes observed being due to chance cannot be excluded.

SUMMARY

The effects on the liver of dextran given by vein to 23 patients in 1-, 2-, and 6-liter infusions, as measured by tests of liver function, have been studied.

A few patients showed moderate changes suggesting possible impairment of liver function after dextran administration. However, similar changes occurred as frequently in patients in a control group of 15 who had not received dextran. Hence, no conclusive evidence of a deleterious action on the liver, either immediate or deferred, could be established.

Polyvinylpyrrolidone administered by vein to 15 patients in 1- or 2-liter quantities, when tested in the same way, also seemed to be without ill effects on the liver.

No ill effects were observed clinically after the infusion of either dextran or polyvinylpyrrolidone, with a single questionable exception involving polyvinylpyrrolidone.

EFFECTS OF FIFTY PER CENT GASTRECTOMY ALONE AND COMBINED WITH VAGOTOMY

Comparison of Gastric Secretory Responses in Esophageal-Fistula Dogs and Man; Landmarks for Fifty per Cent Resection

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AND
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A STANDARD routine for studying the effects of various surgical procedures upon the acidity of the gastric contents of ulcer patients has been used in this clinic for several years. Previous reports [1] have dealt with gastric acidity under fasting (basal) conditions and in response to neurogenic and chemical stimuli in normal persons and in ulcer patients. Secretory responses have been studied before and after gastric resections of various extent, alone and combined with sympathectomy or vagotomy. The clinical and laboratory results following removal of approximately 50% of the stomach combined with vagotomy indicate that of all the combinations studied, the best protection against the development of gastrojejunal ulceration is afforded by this operation.

Similar investigations on dogs have been carried out simultaneously with the clinical studies. Previous papers from the experimental laboratory discussed the assessment of gastric secretory responses in general,[2] the effects of 50% gastrectomy combined with sympathectomy, and the effects of 80% gastrectomy alone and combined with sympathectomy.[3]

Since the requisites of a good ulcer operation seem to be best satisfied in the group of 18 patients treated by 50% gastric resection plus vagotomy,[1b] it was decided to investigate this combination on dogs, in which the extent of resection

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From the Surgical Service and the Smithwick Foundation of the Massachusetts Memorial Hospitals and the Department of Surgery of Boston University School of Medicine.

1. (*a*) Smithwick, R. H., and Kneisel, J. J.: The Effect of Resection of the Sympathetic and Parasympathetic Innervation of the Stomach upon Gastric Acidity, Rev. Gastroenterol. **17**:439, 1950. (*b*) Farmer, D. A.; Howe, C. W.; Porell, W. J., and Smithwick, R. H.: The Effect of Various Surgical Procedures upon the Acidity of the Gastric Contents of Ulcer Patients, Ann. Surg. **134**:319, 1951.

2. Howe, C. W.; Porell, W. J., and Ware, P. F.: Assessment of Gastric Secretory Responses in Relation to Peptic Ulcer: Method of Study and Control Data on 39 Normal Dogs, A. M. A. Arch. Surg. **63**:234, 1951.

3. Effects of Sympathectomy Alone and Combined with Gastrectomy on Gastric Secretory Responses: Experimental Study on Esophageal-Fistula Dogs, with Normal Stomachs, ibid. **64**:238, 1952.

can be more accurately estimated.[3] We wished to augment the data from this small group of patients and to determine (1) whether the results observed in man could be duplicated in animals and (2) what proportion of the acid-lowering effect was due to the gastrectomy phase as opposed to the vagotomy phase of the operation.

This article gives the results of studies on a series of eight normal dogs carried out before and after 50% gastric resection and repeated after the addition of vagotomy and discusses the results in relation to those previously reported for human patients.

METHOD OF STUDY

Gastric secretions were collected through esophageal fistulas from eight normal mature dogs weighing from 5 to 15 kg. By this method [4] the stomach is left in its physiological state, the animal eats normally, and the fistula is continent except for slight loss of saliva. The secretory study routine is essentially the same for human and canine subjects and has been described and discussed elsewhere in detail.[5] Care is taken to have all subjects mentally at ease when the tests are conducted. Gastric juice is obtained by continuous suction from a Stedman pump through a Levin tube, and samples are collected as follows:

1. *Fasting Basal Test (Physiological Neurogenic Stimulation).*—Six continuous suction specimens are collected in 10-minute aliquots.

2. *Insulin Test (Potent Neurogenic Stimulation).*—This test is begun immediately after the completion of the basal run. The drug is administered intravenously to patients in dosage of 0.08 units a pound (1 unit per kilogram for dogs), after which specimens are collected at half-hour intervals for three hours. Blood is withdrawn for sugar determinations prior to and at three half-hour intervals after administration of insulin.

3. *Broth Test (Physiological Chemical Stimulation).*—On a subsequent day, after a repetition of the basal tests as described, 80 cc. of peptone-beef broth is instilled into the stomach via the collection tube (40 cc. for dogs). After 20 minutes the remaining broth is aspirated, and six aliquots are collected at 10-minute intervals.

4. *Histamine Test (Potent Chemical Stimulation).*—Finally the subject is given 0.2 cc. of histamine acid phosphate (0.1 cc. for dogs) subcutaneously, and secretions are collected at 10-minute aliquots for one hour.

This method of study is designed for assessing clinically the gastric secretory responses and for indicating the relative changes caused by various surgical procedures; it does not lend itself to the collection of absolute physiological data.[6]

EFFECTS OF FIFTY PER CENT GASTRECTOMY ON DOGS

Following construction of the esophageal fistula, studies were begun when the wounds had fully healed and the dogs were eating a normal diet. Animals were trained to lie at ease during the tests,[2] and each animal was used as its own preoperative control. When successive trials yielded figures within the same general range for each type of stimulus, the averages of two or three runs were considered

4. Ware, P. F., and Howe, C. W.: Experimental Esophageal and Pharyngocervical Fistula, A. M. A. Arch. Surg. **63**:229, 1951.

5. Farmer and associates.[1b] Howe and associates.[2]

6. Several changes in the study routine have recently been made as a result of experience to date. Samples during the 1-hour basal and broth periods are now collected in three 20-minute aliquots. The insulin period has been shortened to two hours, during which four half-hour aliquots are collected. Representative samples from each period are used for pepsin determinations. The histamine test has been omitted. All tests are run on the same day.

acceptable data. When successive trials showed variations in the result, the average of a larger number of runs on the same animal was used.

A total of 45 basal, 23 broth, 22 histamine, and 13 insulin control runs were completed. After data on these were obtained, each dog was subjected to 50% gastrectomy (by weight) estimated according to a method previously described.[3] Resections were Hoffmeister-type aseptic procedures performed with the Smithwick clamp,[7] a short proximal loop gastrojejunostomy being used. When the dog had recovered from the operation and was eating normally, usually within 10 to 14 days, the studies were repeated. A total of 28 basal, 13 broth, 13 histamine, and 11 insulin postoperative runs were obtained. The average 10-minute pH, volume, and free-acid values for each dog were calculated and the resultant average values for all eight dogs in turn averaged, the results giving the composite 10-minute figures for the series. These are charted in Figure 1, which shows considerable postoperative reduction in acid under basal conditions and after all types of stimulation. It is

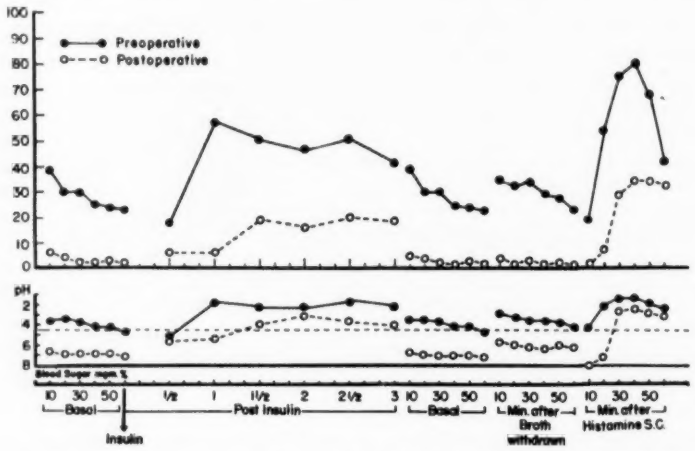

Fig. 1.—Composite graph of free acid and pH before and after 50% gastric resection in eight dogs. Averages of 45 basal, 23 broth, 22 histamine, and 13 insulin runs done preoperatively and 28 basal, 13 broth, 13 histamine, and 11 insulin runs done postoperatively.

apparent that not all animals were rendered completely "achlorhydric" by the operation; some acid response to insulin and histamine was obtained postoperatively during all tests. With this procedure the average pH remained consistently above 4.5 during basal and broth periods. We consider this to be within the safe range in regard to peptic activation. During insulin and histamine stimulation tests, however, the average pH fell to levels dangerously below 4.5, as can be seen from the inversely plotted pH curve in Figure 1. The effect of 50% gastrectomy on the milliequivalents per hour of free acid secreted after each type of stimulus is shown in the top section of the accompanying table. Intragroup variability is shown by the range of values and distribultion of the degree of reduction in acid output among the individual dogs.

7. Smithwick, R. H.: Total Gastrectomy with Particular Reference to Closed (Aseptic) Esophagojejunostomy, New England J. Med. **237**:39, 1947.

Effect of Various Surgical Procedures upon the Acidity of the Gastric Contents

		Preoperative			Postoperative						
					No. of Subjects Whose Acid Output Fell to						
		No. of Subjects *	mEq. per Hour of Free Acid		0 mEq./Hr.	0.1 But Not to 0 mEq./Hr.	0.3 But Above 0.1 mEq./Hr.	1.0 But Above 0.3 mEq./Hr.	3.0 But Above 1.0 mEq./Hr.	% Mean Drop	Range of % Drop
			Mean	Range							
8 dogs	Basal	8	0.70	0.1- 1.4	..	5	3	..	..	89	26- 98
50% gastrectomy	Broth	7	0.64	0.3- 1.2	1	2	4	..	..	84	71-100
	Histamine	8	2.59	0.9- 6.5	..	1	..	4	3†	70	24†- 90
	Insulin	7	2.10	1.1- 4.8	..	..	2	4	1‡	69	64‡- 92
7 dogs	Basal	7	0.64	0.1- 1.4	3	3	1	..	..	93	84-100
50% gastrectomy	Broth	6	0.67	0.3- 1.1	5	1	..	..	..	99	86-100
plus vagotomy	Histamine	6	1.64	0.9- 3.3	..	1	..	5	..	81	59- 95
	Insulin	6	2.33	1.1- 4.8	4	1	1	..	..	98	95-100
18 humans §	Basal	17	4.63	0.1-14.9	10	3	2	2	..	98	75-100
50% gastrectomy	Broth	16	8.32	1.0-18.5	10	2	1	3	..	98	85-100
plus vagotomy	Histamine	16	15.31	3.2-29.1	6	..	1	7	2	96	72-100
	Insulin	17	10.18	3.6-21.3	12	..	3	2	..	99	91-100
3 dogs	Basal	3	0.33	0.2- 0.4	1	1	1	..	..	80	34-100
High gastrectomy	Broth	3	0.67	0.3- 1.6	..	3	..	..	..	93	91- 98
	Histamine	3	4.48	2.1- 6.7	1	1	..	1	..	95	92-100
	Insulin	1	2.97	.....	1	..	..	..	..	100	.....
6 humans	Basal	6	3.71	1.6- 7.2	3	..	1	2	..	93	63-100
High gastrectomy	Broth	6	4.73	1.2-10.4	4	1	..	..	1	95	28-100
	Histamine	5	11.00	1.0-22.4	3	..	..	..	2‖	83	‖
	Insulin	6	1.89	0.1- 3.3	3	..	1¶	1	1	81	22-100

* When complete (matched) preoperative and postoperative data were not available for any test, the subject was dropped from that test.
† The output of two of these dogs increased: from 1.26 to 1.27 and from 0.87 to 1.61. The range of percentage drops is shown only for the dogs whose output decreased.
‡ The output of one dog increased: from 2.073 to 2.284. The range of percentage drops is shown only for dogs whose output decreased.
§ From Farmer and associates.[15]
‖ The output of both increased: from 0.1 to 2.3 and from 6.2 to 6.6. The output of all others decreased 100%.
¶ The output increased: from 0.08 to 0.26.

EFFECTS OF ADDING VAGOTOMY TO FIFTY PER CENT GASTRIC RESECTION IN DOGS

After completion of the postgastrectomy studies, a transthoracic vagotomy was done on each dog through the bed of the 9th or 10th left rib. The lower 2 to 3 cm. of the vagi and their ramifications were resected supradiaphragmatically, and the cut ends of the nerves were secured with brain clips. After vagotomy the animals became more difficult to maintain nutritionally. Although intravenous infusions and blood transfusions were used as indicated during operation and directly afterward, no fluids were administered parenterally during the day before or during a test run. Diets were supplemented by frequent small feedings of a pablum containing milk, cereals, meat paste, and wheat-germ oil, administered by catheter through the esophageal fistula when necessary. With this type of care, dogs remained in good nutritional status for approximately two weeks following vagotomy. All the post-vagotomy data were collected during this early period, after which anorexia, gastric

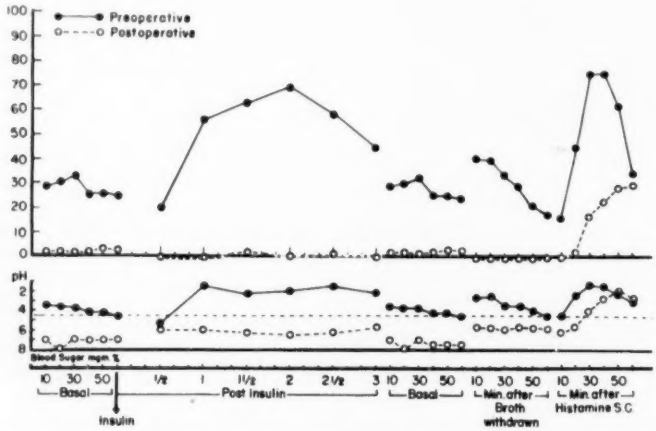

Fig. 2.—Composite graph of free acid and pH before and after 50% gastrectomy and vagotomy in seven dogs. Averages of 41 basal, 22 broth, 20 histamine, and 11 insulin runs done preoperatively and 24 basal, 8 broth, 8 histamine, and 8 insulin runs done postoperatively.

stasis, and emesis led to such progressive nutritional deterioration that data were considered unsatisfactory; all animals died or were killed. One of the original eight dogs died the day following vagotomy. Control data on this animal were discarded and the composite prevagotomy control figures recalculated. This fact accounts for the difference in the control data for the 50% resection as contrasted with the combined procedures. On the seven surviving animals, 24 basal, 8 broth, 8 histamine, and 8 insulin postvagotomy runs were obtained. The composite 10-minute figures are charted in Figure 2, which shows further reduction in acidity for all tests to the point where it was negligible except after histamine stimulation. All pH values were well above the crtical level of 4.5 except after histamine stimulation. It can be seen from the second section of the table that the addition of vagotomy caused reduction in the milliequivalents per hour of acid secreted considerably below the levels obtained with 50% gastrectomy alone.

COMMENT

A satisfactory ulcer operation should reduce the intragastric corrosive digestive power below the level of ulcer activation. In a medium whose pH is 4.5 or over, peptic activity is negligible.[8] It would seem, therefore, that if the pH of the gastric contents could be maintained above this critical level of pH 4.5 during the basal period and after broth and insulin stimulation, the likelihood of peptic ulceration would be negligible. We doubt that the histamine test has any meaning in this respect, since this stimulus probably has no reasonable clinical counterpart.

In this small series of carefully studied dogs, 50% gastrectomy brought the average pH above this critical level during basal periods and broth stimulation, but not for insulin and histamine. In order that the degree of acidity reduction and elevation of pH reported here for 50% resection may not be falsely misleading, we wish to emphasize the following facts previously pointed out.[3] The base-line pH levels are relatively high in our dogs with normal, surgically intact stomachs and resemble data collected from normal humans, whereas in total-pouch dogs (as in peptic ulcer patients) the base-line levels are much lower. It would seem logical to speculate, therefore, that in pouch dogs (or ulcer patients) one would not expect 50% gastrectomy to bring the average pH above the critical level of 4.5 for any of the tests, because the base-line pH level is so much lower to start with than it is in our dogs. It might, however, be expected to lower the acid output per hour to some extent. In four peptic ulcer patients reported by Smithwick and Kneisel,[1a] 50% gastrectomy caused reductions in average total milliequivalents of acid per hour of the same general order of magnitude as reported here for dogs and maintained the pH at a safe level except after histamine. These patients were chosen for this operation, however, because of their relatively low initial acid values. Other data in the same report show that in patients with higher initial levels, estimated two-thirds to four-fifths resections did not always maintain the pH constantly above 4.5. In the treatment of peptic ulcer patients, therefore, the effect of 50% gastrectomy would not appear to be sufficient to maintain the pH above what is considered a safe level for the prevention of ulcer activation, except perhaps in certain rather unusual patients in whom the preoperative level of acid secretion is relatively low.

The addition of vagotomy on the dogs with 50% resection resulted in further reduction in acid output following all types of stimulation. The response to insulin hypoglycemia was obliterated except for minimal amounts of acid in two animals. The reductions following the combined procedure were such that the pH remained constantly well above the critical level of pH 4.5 throughout all tests, except for a slight response to histamine. The early postoperative results of the combined operation on dogs were equaled only by those previously published for 80% gastrectomy,[3] both procedures causing "achlorhydria" in the basal, broth, and insulin tests; the percentage mean reductions in total milliequivalents per hour were similar.

The last three sections of the table compare previously reported data on human patients,[1b] rearranged according to the statistical method used here, with our data

8. Porell, W. J., and Howe, C. W.: Assessment of Gastric Acidity and Pepsin in Relation to Peptic Ulcer: I. Acidity of Gastric Contents, Boston M. Quart. **2**:73, 1951. Farmer and associates.[1b]

on animals for the combined procedure and for high subtotal gastrectomy. They show that the results for 50% gastrectomy plus vagotomy were as good as those for high resection and that the laboratory findings by this method of study for dogs and man are comparable in this small series of subjects.

Following the vagotomy phase of the operation in dogs, vomiting and nutritional disturbances resulted from the characteristic hypertonic paralysis of the vagus-denervated gastric musculature seen in animals. The combined procedure in man, however, has been relatively free of the disagreeable side-effects of either high gastric resection or vagotomy, as will be discussed hereafter.

COMMENT ON USE OF FIFTY PER CENT GASTRECTOMY WITH VAGOTOMY IN HUMAN PATIENTS

Approximately 50% as the optimal amount of stomach to be resected when the maneuver is to be combined with vagotomy was selected at first because it seemed reasonable to expect that gastrectomy of lesser magnitude when combined with vagotomy would reduce acid output as effectively as a more radical gastrectomy alone. This choice was later substantiated by studies on two groups of patients,[1b] one in which resections were less than an estimated 50% and another in which they were considerably greater. Data on six patients in whom no more than one-third of the stomach was removed in conjunction with vagotomy showed that pH values reached dangerous levels on occasions. Studies following high resections with or without vagotomy showed no better results than in the group who had 50% resection plus vagotomy. Fifty per cent resections are easier to perform than high subtotal gastrectomy and should be associated with a lower morbidity and mortality rate in the hands of the average surgeon.

Eight patients treated with the combined procedure followed from one to three years have been notably free of the symptoms of weight loss, food intolerance, weakness, and dumping syndrome, commonly associated with high resections, and of gastric stasis and diarrhea, which so frequently follow vagotomy. On the other hand, several patients treated with vagotomy plus gastroenterostomy have had severe and prolonged postoperative stasis. Fifty per cent resection plus vagotomy appears to be particularly suitable when studies show the chemical and neurogenic responses to be roughly equivalent. In cases with relatively low initial acid levels in which the broth response (chemical factor) outweighs the insulin response (neurogenic factor) we have tended to favor high subtotal gastrectomy. A marked preponderance of the neurogenic factor or situations in which duodenal stump management is particularly hazardous might make gastroenterostomy plus vagotomy the method of choice. Our experience indicates, however, that the majority of cases are suitable for 50% resection plus vagotomy.

When dealing with the changes in acid secretion after gastric resections of various extent, it is desirable to group the subjects according to the level of resection. It would be ideal from the physiological standpoint to group them somehow according to the number of parietal cells left behind in the gastric remnant. As discussed in a previous paper,[3] the most commonly used criterion—the surgeon's estimate at the time of operation—is subject to considerable error. In search of a better yardstick for laboratory use, we performed autopsies on 36 freshly killed dogs weighing

between 5 and 15 kg. and found that the mean ratio of stomach weight to total body weight was 0.95%. This information enabled us to reduce errors of estimation by weighing the specimen at the time of operation. This formula is not applicable to dogs except within the specified weight range, nor is it applicable to man.

In attempting to estimate more accurately the extent of gastric resection in patients, we have followed the lead of Visick [9] in using vascular landmarks. Human stomachs in fresh autopsy specimens have been studied with a view toward selecting points on both curvatures for 50% resection. After random trial on several specimens the following landmarks were chosen: a point on the greater curvature at the junction of the gastroepiploic vessels and a point on the lesser curvature 1 cm. rostral to the lowest major vein cluster contributing to the coronary system. The junction of the gastroepiploic vessels on the greater curvature is readily recognized. At this point the vessels approximate the stomach wall most closely and their branches are slightly divergent. The veins are more readily visible than the arteries in the surgical specimen. The variability of the venous pattern on the lesser curvature makes this point the less reliable of the two. Fortunately, however, because the lesser curvature is so much shorter than the greater, some variance in the selection of this point will not affect greatly the weight of the stomach resected. Eleven normal stomachs were divided between these landmarks at autopsy, the specimens trimmed of extraserosal fat, the esophagus and duodenum removed at the gastric mucosal junction, and the two halves weighed. In all 11 specimens, the distal portions weighed 50% (+ or — 5%) of the total stomach weight. This observation, of course, does not prove that the weight of the resected specimen bears a constant relationship to the amount of parietal-cell-bearing mucosa remaining, but it seems logical that it might. It is also true that these weight relationships, even if confirmed by subsequent studies, might be distorted by the hypertrophy and edema frequently seen in patients with pyloric obstruction. Although this method admittedly falls short of the ideal, we have more confidence in it than in the former procedure of guessing at the extent of resection. Operations in which these landmarks are used yield resected specimens which include all the smooth prepyloric mucosa distally, with a 2 or 3 cm. rim of corrugated mucosa proximally.

The greatest drawback to procedures involving resection of the vagus nerves is the hazard that the denervation may not be complete. In the small number of instances in which this occurs, the patient would appear to be at less disadvantage if the vagotomy is combined with 50% resection rather than with a gastroenterostomy.

SUMMARY AND CONCLUSIONS

Fifty per cent gastrectomy on dogs lowered the gastric acid output during fasting periods and after chemical and neurogenic stimulation. The pH was elevated during all test periods but still attained dangerous levels after insulin (and histamine) stimulation. Percentage mean reductions in total milliequivalents of free acid per hour for the various test periods were as follows: basal, 89%; insulin, 69%; broth, 84%; and histamine, 70%.

9. Visick, A. H.: Measured Radical Gastrectomy: Review of 505 Operations for Peptic Ulcer, Lancet **1**:505, 1948.

The addition of vagotomy to 50% gastric resection caused further reduction in acid output, so that the pH remained well above the safe level of 4.5 during all test periods and the animals were essentially achlorhydric except for a slight response to histamine. Reduction in total milliequivalents of free acid per hour occurred to the following degree: basal, 93%; insulin, 98%; broth, 99%; and histamine, 81%.

These results were equaled only by those previously reported as following 80% gastrectomy.

The method of study used in these experiments yields results very much like those similarly obtained in man, and the data reported here for the operation of 50% gastrectomy plus vagotomy on dogs augment and support those previously reported for a group of 18 patients upon whom the same operation was performed.

Certain aspects of the use of 50% gastrectomy with vagotomy in man are discussed with special reference to anatomical landmarks as an aid in judging the amount of stomach to be resected.

SPONTANEOUS RUPTURE OF ESOPHAGUS

Report of a Successful Case with Cardiac Arrest and Review of the Literature

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MACKENZIE,[1] in 1884, defined spontaneous rupture of the esophagus as being a "sudden bursting of the gullet during prolonged and violent vomiting, giving rise to acute pain in the course of the tube with extreme dyspnea, sometimes even to orthopnea, subcutaneous emphysema and to collapse generally ending in death." By qualifying the gullet as normal such definition is applicable today.

We wish to present a review of the literature on this subject and to report a case complicated by cardiac arrest in which treatment was successful. From the literature we have collected 85 cases which we feel fulfill the criteria of spontaneous rupture of the esophagus. The report included herein will make a total of 86. We are also including seven probable instances of spontaneous rupture of esophagus which for one reason or another did not completely fulfill the criteria set down.[2] The details of these have not been included in the computation of our data. This

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Professor of Thoracic Surgery, Georgetown University School of Medicine (Dr. Davis).

1. MacKenzie, M.: Diseases of Nose and Throat, Philadelphia, Blakiston Company, 1884, Vol. 2, p. 169.

2. (*a*) Carter, J. P.; Aldrich, E. M., and Drash, E. C.: Spontaneous Rupture of Esophagus, Surgery **30**:500 (Sept.) 1951, Case 1. (*b*) Christie, G. W.: Unusual Case of Perforated Ulcer of Esophagus, Lancet **2**:17 (July) 1915. (*c*) Frink, N. W.: Spontaneous Rupture of Esophagus: Report of Case with Recovery, J. Thoracic Surg. **16**:291 (June) 1947. (*d*) Gardner, C. M.: Spontaneous Rupture of Esophagus, Arch. Surg. **59**:710 (Sept.) 1949. (*e*) Monro, A.: Morbid Anatomy of the Human Gullet, Stomach, and Intestines, Philadelphia, George Ramsay, 1811, p. 311. (*f*) Moore, J. A., and Murphy, J. D.: Spontaneous Rupture of Esophagus: Case with Recovery, J. Thoracic Surg. **17**:632 (Oct.) 1948. (*g*) Robson, L. C.: Perforation of Esophagus Following Burns, Brit. M. J. **1**:414 (April) 1943.

review includes only those cases published in the English language, with one exception, the case of Boerhaave. This case is quoted by Barrett [3] and represents the first known case reported in any language.

We have made careful examinations in approximately 70 other cases in which the condition was purported to be spontaneous rupture but have excluded these on various grounds. On close examination they were found to be traumatic perforation, esophageal ulcer, foreign bodies, external trauma, instrumental perforation, syphilitic periarteritis, vomiting of pregnancy, esophageal stricture, carcinoma of the esophagus, or associated with cranial lesions. For the sake of completeness these articles are quoted in an additional bibliography. The cases are so noted either because the respective author reported them as spontaneous or because other authors included them in their statistics or bibliography. They are also recorded for the benefit of future authors.

The case reported by Fitz,[4] in 1877, has been repeatedly listed as the first case of this condition in the American literature. We feel that this is not a true example of spontaneous rupture for the following reasons: 1. A foreign body was involved. 2. The course was not that of a spontaneous rupture, since the patient lived seven and one-half days without treatment. 3. The tear was at the level of the bifurcation of the trachea and Fitz believed that "such rents are distant from rather than close to the cardiac end of the stomach." 4. Fitz believed the impaction of a foreign body "to be an essential factor." 5. He doubted a case to be spontaneous when there was rupture directly into the pleural cavity.

We wish to suggest that all true cases be reported in the future as "spontaneous rupture." The word "perforation," which is commonly used, suggests a foreign body or instrumentation and should be reserved for such cases as well as for those in which there is preexisting disease.

MECHANISM OF RUPTURE

Spontaneous rupture of the esophagus occurs, as the name implies, without preexisting esophageal disease and in the absence of a foreign body or instrumentation. It has been recognized for centuries that the act of vomiting is intimately associated with this catastrophe. In fact, Dryden,[5] in 1788, stated that "the act of vomiting was the sole cause of this rupture." As will be brought out later, vomiting is not by necessity associated with this condition but is the commonest episode preceding the onset of illness. When vomiting was not noted at the onset, it usually occurred at some time during the course of the disease.

According to the studies of Hatcher and Weiss,[6] vomiting is initiated in the sensory center of the vagus, which is the most essential nerve involved. It supplies inhibitory fibers for the cardiac end of the stomach, which obviously must open so that the gastric contents can be ejected. It controls closure of the pylorus, which occurs at the time of the actual nausea, and, in addition, inhibits the swallowing

3. Barrett, N. R.: Spontaneous Perforation of Esophagus, Thorax **1**:48 (March) 1946.

4. Fitz, R. H.: Rupture of Healthy Esophagus, Am. J. M. Sc. **73**:17 (Jan.) 1877.

5. Dryden, J.: An Account of Rupture of the Esophagus from the Action of Vomiting, M. Commentaries Edinburg **3**:308, 1788.

6. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, J. Pharmacol. and Exper. Therap. **22**:139 (Oct.) 1923.

reflex. Reverse peristalsis must then occur to force the gastric contents into the esophagus. The act of vomiting therefore becomes a highly complicated mechanism mediated through the sensory center of the vagus.

It is postulated that two mechanisms for derangement of the act of vomiting may occur in affected persons: 1. As a result of repeated stimuli the vomiting center may become fatigued. 2. Owing to a confused mental state there may be poor coordination of the mechanism during the actual act of vomiting. Either or both these factors may be present, particularly in patients recovering from an acute bout of alcoholism.

Mallory and Weiss felt that with sudden ejection of the gastric contents into the esophagus, the esophagus and diaphragm might fail to relax at the same moment and the gastric contents would be forced at increased pressure into a closed tube.[7] This last step is probably the more important, for it has been stated by MacKenzie [1] that rupture occurs only when the vomitus cannot be expelled from the esophagus at the same rate as it is received from the stomach. In such circumstances the esophagus would be suddenly distended at a great pressure and the tube would become, in effect, a blind one, and rupture would then occur at its weakest point. Clinical proof of such a mechanism is found in the case reported by Smead [8] in which the patient had vomiting due to gangrenous bowel. This patient also had a stricture in the lower third of the esophagus. With "strenuous vomiting for two hours" rupture of the esophagus occurred immediately below the stricture. This is an indication of what might happen when the gastric contents cannot leave the esophagus as rapidly as they entered it.

Numerous studies have been performed both in the animal and in fresh autopsy specimens to discover the weak point of the esophagus. MacKenzie,[1] Zenker and Von Ziemssen,[9] Burt,[10] and Hertzog [11] found the weakest point of the esophagus to be its lowest third. The pressure necessary to produce rupture varied from 3.6 to 4.8 lb. (1.6 to 2.2 kg.) per square inch. In all cases studied the esophageal tear occurred in a longitudinal direction. It was Hertzog's [11] impression that the pressure necessary to rupture the human esophagus could easily be produced in the act of vomiting.

Spontaneous rupture of the esophagus may also result from a sudden rise in pressure within the gastrointestinal tract during defecation,[12] while lifting weights,[13] or during induction or recovery from anesthesia.[14]

7. Mallory, G. K., and Weiss, S.: Hemorrhages from Lacerations of Stomach Due to Vomiting, Am. J. M. Sc. **178**:506 (Oct.) 1929. Hatcher.[6]

8. Smead, L. F.: Spontaneous Rupture of Esophagus Following Vomiting, Am. J. Surg. **13**:497 (Sept.) 1931.

9. Zenker, F. A., and Von Ziemssen, H.: Cyclopedia of the Practice of Medicine, New York, William Wood & Company, 1878, Vol. 8, p. 90, Cases 1 and 6.

10. Burt, C. A.: Pneumatic Rupture of Intestinal Canal, Arch. Surg. **22**:875 (June) 1931.

11. Hertzog, A. J., and Leighton, R.: Spontaneous Perforation of Esophagus, Minnesota Med. **29**:442 (May) 1946.

12. (*a*) Beal, J. M., Jr.: Spontaneous Rupture of Esophagus, Ann. Surg. **129**:512 (April) 1949. (*b*) Eggers, C., and Maier, H. C.: Nelson's New Loose-Leaf Surg., Vol. 4, p. 155.

13. Rolleston, H. D.: Rupture of Esophagus: Abscess in the Posterior Mediastinum Bursting into the Left Pleura; Pyopneumothorax; Death, Tr. Path. Soc. London **45**:58, 1894.

14. Roy, D. W.: Case of Rupture of Esophagus, Lancet **2**:1765 (Dec.) 1911.

The high incidence in alcoholics is frequently mentioned in the literature. We feel that this has been assumed but not proved. In our review we found 29 persons who were known alcoholics or who had taken varying amounts of alcohol prior to the onset. In 12 instances the person had recently ingested a heavy meal. Four had had a heavy meal and alcohol. The number of cases in our perusal of the literature in which there was no mention of alcohol or a heavy meal prior to onset numbered 42, nearly 50% of the series. It seems certain that if the history of alcoholism had been known it would have been mentioned. For this reason we feel that alcoholism per se has been overrated as an etiologic factor in previous writings. We believe that any mechanism which causes prolonged vomiting, fatigue of the vomiting center, or distortion of the act of vomiting may cause rupture of the esophagus.

McWeeney,[15] in 1900, was perhaps the first to recognize an inflammatory infiltration in the area of rupture. Although he recognized the significance of a sudden increased pressure within the esophagus, coupled with poor coordination, as an etiologic factor, he was the first to realize that esophagitis may be a necessary preceding state. Kinsella [16] has pointed out the difficulty of recognizing a local esophagitis following this catastrophe, since by necessity an inflammatory reaction occurs about the site of rupture. Kinsella and Graham [17] have also felt that a preceding local esophagitis may in some way contribute to the weakness of the esophagus in its lowest third.

AGE, SEX, AND RACE

In this review, the average age of the patients was 46 years, with a range from 5 months [18] to 76 years.[19] There were 68 males, 14 females, and in four patients the sex was not mentioned. There were 66 white patients, 6 Negro patients, and in 14 the race was not noted.

SIGNS AND SYMPTOMS

The signs and symptoms of this condition immediately present the physician with an obvious medical emergency. We will present a description of these signs and symptoms in conjunction with statistical data from our review.

Symptoms.—The presenting symptoms are tabulated in Table 1. The commonest combination of presenting complaints were epigastric and chest pain.

A. Pain: Pain was commonest in the epigastrium and next commonest in the lower parts of the left side of the chest. Occasionally, it was substernal. In rare instances it radiated to the back. The pain is characteristically excruciating and is rarely relieved by a single injection of a narcotic. In seven patients the pain was described as a bursting or tearing sensation. (In one, the pain was of such severity

15. McWeeney, E. J.: On Rupture of Apparently Healthy Esophagus, Tr. Roy. Acad. Med. Ireland **18**:393, 1900.

16. Kinsella, T. J.; Moore, R. W., and Hertzog, A. J.: Spontaneous Rupture of Esophagus, J. Thoracic Surg. **17**:613 (Oct.) 1948.

17. Graham, E. A.; Singer, J. J., and Ballon, H. C.: Surgical Diseases of Chest, Philadelphia, Lea and Febiger, 1935, p. 377.

18. Menne, F. R., and Moore, C. U.: Case of Rupture of Esophagus in Infant, Arch. Pediat. **38**:672 (Oct.) 1921.

19. Mehn, W. H.: Spontaneous Rupture of Esophagus, Proc. Inst. Med. Chicago **16**:422 (March) 1947.

that there was a feeling of impending death.[2a]) Pain persists as the most striking feature of the disease. It is as common as vomiting but far more important since it lasts longer.

B. Vomiting: Although vomiting may occasionally be present for days, in other cases, such as our own, a single act of vomiting may be all that is noted. In some instances vomiting disappears with the initial outburst of pain. As important as vomiting is the act of retching. In some patients who were unable to actually eject the contents of the stomach, persistent retching was noted.

Pain and vomiting are the commonest, severest, and most persistent symptoms noted by the patients and are the prime reasons for their seeking medical advice.

C. Hematemesis and Thirst: Hematemesis or thirst may be the presenting or initial symptom in a small number of cases, but these symptoms do not assume the importance of pain or vomiting. Thirst as an early symptom is not as common as it has been quoted to be by early authors.

Signs.—A. Shock and Cyanosis: The shock at onset varied from mild to severe and progressed rapidly with the passage of time. Although shock was seen in 70%

TABLE 1.—*Presenting Symptoms*

Epigastric pain	37
Vomiting	38
Chest pain	28
Epigastric and chest pain	17
Dyspnea	7
Hematemesis	2
Shock	2
Weakness	1
Unknown	3

of cases, its absence does not preclude the diagnosis of spontaneous rupture of the esophagus.

In no patient was cyanosis the intial or presenting symptom, and in many it was a late manifestation.

B. Subcutaneous and Mediastinal Emphysema: Subcutaneous emphysema is not always an early physical finding in spontaneous rupture of the esophagus and was a late development in some of the patients studied. Since it is not a necessary sign and may be present only late, waiting for its appearance is unwarranted and may delay surgery until the patient is inoperable because of physical deterioration. In cases in which rupture occurs directly into the pleural cavity rather than first into the mediastinum, emphysema may be completely absent.

Obviously, if emphysema is to occur, it will be first noted in the mediastinum. Early examination of chest x-rays for evidence of air in the mediastinum or retrocardiac area is mandatory, since its presence here may antedate subcutaneous emphysema by a number of important hours.

In a number of instances in which emphysema was not recorded, roentgenological diagnosis was not yet available. However, in many of these the actual postmortem examinations are complete in other details. Again, since emphysema is a sign which is regarded as specific in the literature, the fact that it is not mentioned in 32 cases is significant. We wish to stress that its presence is not necessary for making a

diagnosis of spontaneous rupture of the esophagus. It may occur late in the course of the illness and, further, it may never occur.

C. Abdominal Rigidity and Tenderness: The high incidence of both abdominal tenderness and rigidity should be noted (Table 2). Frequently, an incorrect diagnosis of ruptured peptic ulcer was made, leading to unsuccessful and unnecessary exploratory laparotomy. The presence of abdominal symptoms and signs should make the physician suspicious of a diagnosis of ruptured peptic ulcer when these are coupled with abnormal physical findings in the chest. Although it is true that as time progresses the abdominal symptoms become less in magnitude and those referable to the thorax greater, much valuable time is lost if the illness is allowed to proceed to this stage.

D. Chest Signs: The absence of abnormal chest signs was more frequent in the early literature. Until the past two decades, a clinical diagnosis of the condition was extremely rare. The usual diagnosis in these cases was either ruptured peptic ulcer or myocardial infarction or shock of unknown origin, and the true disease was not discovered until autopsy.

TABLE 2.—*Individual Symptoms and Signs*

Symptom	Present	Absent	Unknown
Pain	78	..	8
Vomiting or retching	75	2	9
Hematemesis	16	15	55
Thirst	13	6	67
Sign			
Shock	57	16	13
Cyanosis	26	18	42
Emphysema	44	10	32
Abdominal tenderness and/or rigidity	58	13	35
Chest signs	50	7	29

When the initial examination of the chest reveals no abnormalities, the examination should be repeated frequently because the evolution of positive signs is rapid, and so that changes which occur within a short period of time will not be missed. Reexamination delayed 12 or 24 hours after the patient is first seen may be the difference between a thoracotomy and cure and the realization that a patient's condition is so deplorable that only supportive measures can be attempted.

Abnormal chest findings recorded in the series are shown in Table 3. These positive signs were noted either by physical or by roentgenological examination of the chest.

The high incidence of hydropneumothorax requires some comment. Some authors have proposed that mediastinitis and mediastinal bulging result from rupture of the esophagus and subsequent ejection of the gastric contents into the mediastinum. This is followed by rupture into the free pleural space. The incidence of hydropneumothorax at an early stage in the disease process would indicate that this mechanism is not always present and that there may be direct perforation into the pleural space. Hydropneumothorax will occur later in patients when mediastinitis develops first. There is no question, however, that diagnosis has been made and treatment given in cases in which only mediastinitis or mediastinal collection of fluid was noted.

When hydropneumothorax develops early, subcutaneous emphysema appears late or not at all. In the case herein reported the x-ray diagnosis was hydropneumothorax without mediastinal emphysema. X-rays taken prior to surgery (approximately 22 hours after onset) still showed no evidence of mediastinal collection of fluid. The absence of mediastinal or subcutaneous emphysema leads us to believe that there was direct perforation into the free pleural space.

In positive findings it is worth while to note the large number of thoracic entities which may be encountered either by physical examination or by x-ray study. These varied from a normal x-ray to mediastinal fluid, pleural effusion, hydropneumothorax, and bilateral pneumonia. Therefore, the physician must always have this condition in mind in the diagnosis of the acutely ill medical patient who presents himself with a combination of thoracic and abdominal signs and symptoms.

TABLE 3.—*Chest Findings on Physical and/or X-Ray Examination*

Left hydropneumothorax	17
Left pleural effusion	12
Mediastinal emphysema	9
Left pneumothorax	3
Right pleural effusion	2
Right hydropneumothorax	2
Bilateral hydropneumothorax	2
Normal x-rays	2
Bilateral pleural effusion	1
Mediastinal fluid	1
Left empyema	1
Bilateral pneumonia	2

SURGERY

Of the 86 patients 45 had some kind of surgical procedure performed. Although thoracentesis was done on only 17 patients we believe that any treatment directed toward the thoracic calamity will aid in the prognosis.

Various types of operations were used. For obvious reasons some patients had more than one operation. In recent years with a more acute appreciation of the problem, thoracotomy has been performed, and this was noted in 18 cases. In 13 cases exploratory laparotomy was performed, with a preoperative diagnosis of ruptured peptic ulcer. In several others, although abdominal exploration was planned, the poor condition of the patient precluded any surgical attempt. The abdominal findings at the time of laparotomy revealed no abnormalities, except in several instances in which a small amount of free peritoneal fluid was found. It seems evident that abdominal surgery may hasten the death of the patient.

In one case (Foggitt,[20] 1946) an esophageal rupture was correctly diagnosed before operation and was approached subdiaphragmatically. The esophagus was pulled into the abdominal cavity and sutured. The repair was unsuccessful, and at autopsy mediastinitis was found. We believe that this case indicates that only transthoracic repair offers these patients any hope of recovering. The abdominal approach does not provide adequate drainage of the mediastinum.

20. Foggitt, K. D.: Case of Spontaneous Perforation of Esophagus, Brit. J. Tuberc. **40**:133 (Oct.) 1946.

In 7 patients intercostal catheters were inserted, and in 10 rib resections and drainage of an empyema were performed. One patient received a mediastinotomy. Adjunct procedures were also done on these patients, including jejunostomy in three and gastrostomy in one.

In several cases the rupture was a postoperative complication of such procedures as hysterectomy,[21] repair of a strangulated hernia,[22] and amputation of a leg and craniotomy.[14] In the last case mentioned, improper administration of anesthesia was thought to be the cause of the rupture. This patient had copious vomiting and retching during the induction of anesthesia for the amputation of a lower extremity, and it is probable that the esophagus ruptured during this induction.

SIDE OF TEAR

In the majority of patients the tear has occurred in the left side of the esophagus. It has been experimentally shown that the tear occurs in the lower third of the esophagus, but one may conjecture as to why the left side is more frequently involved. Barrett has given the following reasons for this and we will quote directly from him:[3]

> The left side of the esophagus is much more commonly affected than the right, presumably because at the extreme lower end the right side is supported to some extent by the thoracic aorta and retropericardial fat, while the left lies directly under the parietal pleura. Below the diaphragm the short stretch of the abdominal esophagus is buttressed by the liver tunnel and the fundus of the stomach.

Thomson[23] has used similar reasoning and states that "the lower end of the esophagus is buttressed posteriorly and posteromedially by the vertebrae, anteriorly and anterolaterally by the pericardium, the left posterolateral aspect is thus the only unprotected site."

In our review of the literature we found that the left side was involved in 39 cases, the posterior aspect in 11, the anterior aspect in 4, and the right side in 8. In the remainder of 24 cases the exact side of the rupture was not noted by the author.

LENGTH OF RUPTURE IN THE ESOPHAGUS

In 20 cases the length of the actual tear was not mentioned in the case reports. In the remainder the length varied from 0.6 to 8.9 cm., the average length of rupture being 2.24 cm.

CHEST FINDINGS AT OPERATION OR AUTOPSY

Although chest findings were positive in only 50% of cases reported ante mortem, when details at operation or post mortem were included, it was found that in all cases there were definite pathological findings. There were two major categories of findings. In one, mediastinitis was initially present and later progressed to hydropneumothorax when the mediastinal contents ruptured into the pleura. In the second group hydropneumothorax occurred first, followed in some instances by

21. Barrett, N. R.: Case of Spontaneous Perforation of Esophagus Successfully Treated, Brit. J. Surg. **35**:216 (Oct.) 1947.

22. Boyd, S.: Rupture of Esophagus in Case of Addison's Disease, Tr. Path. Soc. London **33**:125, 1882.

23. Thomson, J. D.: Spontaneous Perforation of Esophagus, Brit. M. J. **1**:151 (April) 1950.

loculated empyema. Williams and Boyd [24] have emphasized that the amount of liquid material found in the chest was not necessarily just gastric contents but to a large extent was the result of a profuse outpouring of fluid from the pleura as a normal reaction to injury.

Although we have not specifically listed the findings in the pleural cavity at the time of surgery or at autopsy, authors have repeatedly mentioned the presence

TABLE 4.—*Chest Findings at Time of Surgery or Post Mortem*

Left pleural effusion	28
Mediastinitis	26
Left hydropneumothorax	17
Right pleural effusion	7
Bilateral pleural effusion	7
Left pyopneumothorax	3
Right hydropneumothorax	2
Bilateral hydropneumothorax	3
Periesophageal abscess	2
Empyema (site unmentioned)	2
Right empyema	1
Bilateral empyema	1
Left hemothorax	1
Bilateral pneumothorax	1
Right pyopneumothorax	1
Bilateral pyopneumothorax	1

TABLE 5.—*Diseases Associated with Esophageal Rupture*

Duodenal ulcer [25a-g]	8
Gastric ulcer [25h-l]	3
Tuberculosis [25k]	1
Dyspepsia [25b, i]	2
Pyelonephritis [12a]	1
Asthma [21]	1
Addison's disease [22]	1
Questionable peptic ulcer [20]	1
Strangulated hernia, peritonitis [22]	1
Arteriosclerotic heart disease [25b, p]	2
Carcinoma of stomach [25q]	1
Poliomyelitis [16]	1
Carcinoma of prostate [25j]	1
Syphilitic aortitis [25k]	1
Nephritis [25b, r]	2

of undigested particles of food, or barium, or the odor of alcohol. While bacteriological examinations were not reported in many cases, it is to be taken as an accepted fact that the vast majority of these effusions were infected. Cases in which gross infection might be escaped would be those in which rupture was into the mediastinum and at the time of surgery or autopsy the rupture had not actually perforated either pleural cavity.

The actual recorded findings are summarized in Table 4.

24. Williams, T. H., and Boyd, W.: Spontaneous Rupture of Esophagus, Surg., Gynec. & Obst. **42**:57 (Jan.) 1926.

ASSOCIATED DISEASES

The diseases of importance associated with this condition were those which predisposed to prolonged vomiting. For example, carcinoma of the stomach producing pyloric obstruction with continuous vomiting would predispose to rupture the esophagus. Table 5 lists the associated disease which we have culled from the literature.[25] In most instances there was no associated systemic disease, or the disease was usually unimportant from an etiologic standpoint.

DIFFERENTIAL DIAGNOSIS

1. *Ruptured Peptic Ulcer.*—Perforation of such an ulcer is perhaps the commonest misdiagnosis. The following several points should be noted which will be of value in the proper diagnosis of ruptured peptic ulcer: (1) absence of a previous ulcer history; (2) violent and occasionally repeated vomiting; (3) excruciating pain; (4) absence of free air under the diaphragm, as seen roentgenographically; (5) the presence of surgical emphysema, and (6) the presence of respiratory symptoms such as dyspnea and cyanosis.

2. *Myocardial Infarction.*—This condition may be differentiated from rupture of the esophagus in the following several ways: (1) if there is a history of previous heart disease, (2) if the pain is typically located in the substernal area, and (3) if the type of pain is described as pressing or squeezing in infarction. A normal electrocardiogram is found in spontaneous rupture of the esophagus. Abnormal findings on examination of the chest or by chest x-rays are more likely to be found in spontaneous rupture of the esophagus than in myocardial infarction.

3. *Bronchopleural Fistula.*—In instances of bronchopleural fistula, vomiting, if present, will be a minor symptom. The usual complaint is of a severe cough productive of large quantities of sputum. The aspiration of the pleural contents and the instillation of methylene blue will result in the expectoration of the dye. After the diagnosis of a bronchopleural fistula has been established, aspiration of the chest usually reveals pus. In spontaneous rupture of the esophagus, the gastric contents can usually be recognized or suspected on pleural aspiration.

4. *Acute Pancreatitis.*—In cases of acute pancreatitis the history is again of prime importance. These patients may have a history of alcoholism, the character of the pain may be similar, and vomiting occurs frequently in both conditions. The two chief aids are (1) chest x-ray studies and (2) serum amylase or urinary dias-

25. (*a*) Hertzog.[11] (*b*) Kernan, J. D.: Perforation of Esophagus as Surgical Emergency, S. Clin. North America **30**:405 (April) 1950. (*c*) Kinsella.[16] (*d*) Kinsella, T. J.; Moore, R. W., and Hertzog, A. J.: Spontaneous Perforation of Esophagus, Am. J. Surg. **17**:584 (July) 1951. (*e*) Layne, J. A., and Hildebrand, E.: Rupture of Esophagus During Severe Vomiting, Gastroenterology **13**:171 (Aug.) 1949. (*f*) Mulsow, F. W.: Spontaneous Rupture of Esophagus, ibid. **16**:450 (Oct.) 1950. (*g*) Thomson.[23] (*h*) Beal.[12a] (*i*) Eliason, E. L., and Welty, R. F.: Spontaneous Rupture of Esophagus, Surg., Gynec. & Obst. **83**:234 (Aug.) 1946. (*j*) McLeod, C. E., and Gardner, N.: Spontaneous Rupture of Esophagus: Case Report, Connecticut M. J. **12**:622 (July) 1948. (*k*) Watkins, R. W.: Case of Spontaneous Rupture of Esophagus, Tr. Chicago Path Soc. **11**:23 (June) 1919. (*l*) Adams, W.: Spontaneous Rupture of Esophagus, Tr. Path. Soc. London **29**:113, 1878. (*m*) Barrett.[21] (*n*) Boyd.[22] (*o*) Foggitt.[20] (*p*) Flipse, M. E.: Spontaneous Rupture of Esophagus, Dis. Chest **19**:165 (Feb.) 1951. (*q*) Harrison, C. E.: Case of Rupture of Esophagus, Lancet **1**:784 (Aug.) 1893. (*r*) Schultze, O. H.: Case of Traumatic Rupture of Cardiac Orifice of Esophagus Probably Caused by Violent Vomiting, Proc. New York Path. Soc. **7**:138 (Oct.) 1907.

tase determinations. In cases of acute pancreatitis with pleural effusion seen in this hospital there is usually an elevated amylase value for both blood and pleural fluid.

5. *Spontaneous Pneumothorax.*—In this condition it is unusual to have pleural fluid present at the onset. If present, the aspiration of such a fluid will either reveal clear or, occasionally, bloody contents. Grossly infected pleural effusion is not seen in this particular condition. Vomiting, which is common in spontaneous rupture of the esophagus, is not common in pneumothorax.

TREATMENT

Perhaps the first intelligent method of treatment was suggested in 1900, when Bowles [26] recommended mediastinotomy to be followed by actual suture of the laceration. These same sentiments were again presented approximately 15 years later by Walker.[27]

The method of treatment often suggested is rib resection and gastrostomy. The importance which previous authors have placed on gastrostomy may be gleaned from the fact that as recently as 1948, Jackson [28] recommended this procedure. It appears to us that this method is contraindicated, since any nourishment supplied this way would be immediately regurgitated back into the pleural cavity.

Apparently the first author to attempt surgical repair of the esophagus was Collis [29] in 1944, when he used a thoracic approach for repair in a 41-year-old man. In 1946 Foggitt [30] reported a case in which he used an abdominal approach. Both these attempts, however, were unsuccessful. In 1946 Cummings [30] reported a case in which thoracotomy was done successfully by Overholt. In 1947 Barrett [31] and Olsen and Clagett [31] reported cases in which treatment by open thoracotomy was successful.

To our knowledge five patients have recovered following rib resections alone. Two of these are merely mentioned briefly in an editorial comment by Graham,[32] and the others were reported on by Lynch [33] and Dunavant and Skinner.[34] Frink [2c] has reported on a patient whom we considered to have a probable case of spontane-

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26. Bowles, R. L., and Turner, G. R.: Rupture of Esophagus Caused by Vomiting, Brit. M. J. **1**:763 (March) 1900; abstracted, Med.-Chir. Tr. London **83**:241, 1900.

27. Walker, I. J.: Spontaneous Rupture of Healthy Esophagus, J. A. M. A. **62**:1952 (June 20) 1914.

28. Jackson, C., and Jackson, C. L.: Cyclopedia of Medicine and Surgery, Philadelphia, F. A. Davis Company, 1948, Vol. 6, p. 25.

29. Collis, J. L.; Humphries, D. R., and Bond, W. H.: Spontaneous Rupture of Esophagus, Lancet **2**:179 (Aug.) 1944.

30. Cummings, G. O.: One Hundred Cases of Esophageal Disease, J. Maine M. A. **37**:275 (Nov.) 1946.

31. Olsen, A. M., and Clagett, O. T.: Spontaneous Rupture of Esophagus: Report of Case with Immediate Diagnosis and Successful Surgical Repair, Postgrad. Med. **2**:417 (Dec.) 1947.

32. Graham, E. A.: Editorial Comment, in Graham, E. A., editor: The 1943 Yearbook of General Surgery, Chicago, The Year Book Publishers, Inc., 1944, p. 382.

33. Lynch, J. P.: Spontaneous Perforation of Esophagus, New England J. Med. **241**:395 (Sept.) 1949.

34. Dunavant, D., and Skinner, E. F.: Spontaneous Rupture of Esophagus, Surgery **29**:527 (April) 1951.

ous rupture, who also recovered with rib resection. Thoracotomy, to our mind, is the only specific treatment once the diagnosis has been made.

SUGGESTED PLAN OF DIAGNOSIS AND TREATMENT

1. *History and Physical Examination.*—Onset and details of present illness are of importance in the recording of the history. Specific factors which should be searched for by the examining physician include the following: (1) history of alcoholism; (2) recent ingestion of a heavy meal; (3) antecedent gastrointestinal symptoms; (4) presence of vomiting, including type and frequency, and (5) pain, its quality and distribution, and radiation.

In the physical examination general details must, of course, be noted, such as shock, state of hydration, etc. Specifically, the abdomen and chest require the most attention.

2. *X-Ray Examination of the Chest.*—This is the most single reliable roentgenogram for determining the presence of air under the diaphragm and is usually done routinely in cases of possible ruptured peptic ulcer. The physician should remember to check carefully the lung fields, looking for fluid, mediastinal widening, emphysema, or the presence of air or fluid within the mediastinum.

3. *Thoracentesis.*—When fluid or fluid and air are detected within the pleural cavity, thoracentesis should be immediately performed. The actual odor of the fluid should be noted, since this may give an indication that gastric juice with hydrochloric acid is present. If, for some reason, immediate thoracotomy cannot be performed, the value in repeated aspiration of the chest should be kept in the mind of the physician.

4. *Laboratory Tests.*—These tests should include a blood count, urinalysis, and blood typing and cross matching. Examination of the pleural fluid should include a cell count, differential count, culture, determination of reaction to litmus paper, and test for hydrochloric acid with Töpfer's reagent.

5. *Gastric Suction.*—After aspiration of the chest, a Levine tube should be inserted into the stomach and connected to continuous Wangensteen suction. The patient is refused all nourishment by mouth.

6. *Antibiotic Therapy.*—These patients should be given adequate doses of penicillin and streptomycin immediately. A suggested routine is the injection of 100,000 units of penicillin intramuscularly every 3 hours and 0.5 gm. of streptomycin intramuscularly every 12 hours. Aureomycin or chloromycetin given intravenously could also be used.

7. *Surgery.*—The guiding principle of treatment should be that the chest and mediastinum must be drained and the rupture sutured at the earliest possible time. A full thoracotomy should be done with resection of the seventh or eighth rib. When the pleural cavity is opened, cultures should be taken and the remainder of the pleural material evacuated. In cases in which rupture is into the mediastinum and not into the pleural cavity, rapid drainage of the mediastinum should be carried out. As noted by Lynch and Samson,[35] such decompression of the mediastinum will aid

35. Samson, P. C.: Postemetic Rupture of Esophagus, Surg., Gynec. & Obst. **93**:221 (Aug.) 1951.

in the immediate improvement of the patient's general condition. Such drainage of the mediastinum will require incision of the mediastinal pleura above the actual perforation itself. The esophagus should then be examined for the possibility of preexisting disease and the rupture sutured. It is our feeling that the sutures used should be of a nonabsorbable surgical material, preferably silk. These sutures should be placed in an interrupted manner and at least a two-layer closure performed. Attempts to actually close the perforation with a catgut technique have resulted in some instances in a reperforation. An added safeguard to the line of anastomosis, which was perhaps first used by Clagett, includes suturing a flap of the mediastinal pleura so as to overlap the suture line. This is of theoretical benefit and was performed in our case. The pleura should then be thoroughly irrigated with saline solution and all particles of undigested food scrupulously removed from the pleural cavity.

Penicillin and streptomycin are instilled into the pleural cavity and the cavity drained with an intercostal catheter connected to a waterseal suction. By this method thorough drainage is obtained, since the mediastinum will drain into the pleural cavity. At the conclusion of the procedure bronchoscopy is indicated to enhance reexpansion of the lung on the affected side. In our case this was not done at surgery and had to be performed subsequently. Bronchoscopy at the time of operation probably would have obviated this difficulty.

Postoperatively the general measures for shock are continued and antibiotics, such as penicillin and streptomycin, given. Postoperative care is similar to that used after thoracotomy. This will include postoperative x-rays, removal of the intercostal catheter, encouragement to cough, and appropriate laboratory measures.

8. *Feeding.*—We are not sure of the optimum time for the removal of the Levine tube. Our search of the literature at the time was not helpful in this regard. We continued gastric suction for 10 days in our patient. Actually, we feel this was probably longer than is necessary and we would suggest a period of 5 days in future cases.[36] This part of the postoperative therapy is probably an individual one and will depend on the opinion of the attending surgeon and the pathological findings at the time of surgery. The physician should remember that this is not a simple incision and closure, but rather it is a closure in a grossly infected field.

The administration of antibiotics should be continued until the temperature has remained normal for 48 hours. Probably by the end of five days resistance has developed to streptomycin and after this time other antibiotics may be substituted. If such a case is again encountered by us, we intend to use either aureomycin or chloromycetin intravenously until the patient is able to take these drugs by mouth.

Long-term follow-up tests on these patients should consist of esophagoscopy and barium swallow. If esophageal stricture is proved, dilation of this stricture should be performed. Since peptic ulcer and even carcinoma of the stomach have been associated with some of these cases, we would suggest a complete gastrointestinal series as soon as feasible to rule out associated disease in the upper gastrointestinal tract.

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36. (*a*) Bugden, W. F.: Spontaneous Rupture of Thoracic Esophagus, Am. J. Surg. **83**:225 (Feb.) 1952. (*b*) Samson.[35]

9. *Prognosis.*—Of this total reported series of 86 cases, 68 patients had lesions which proved to be fatal. There are 18 survivals in the English literature, including our patient. Of the patients who survived, all underwent thoracotomy except five. These five, reported on by Graham, Lynch,[33] and Dunavant and Skinner,[34] had a rib resection. Cases in which successful thoracotomy was done have been reported by Barrett,[3] Bugden,[36a] Carter,[2a] Cliffton,[37] Cummings,[30] Kinsella,[16] Lynch,[33] Olsen and Clagett,[31] Samson,[35] Scholefield,[38] and by us.[39] Five patients who had thoracotomy died. One of these patients was reported on by Collis, and this patient died approximately 21 hours after onset. One of Kinsella's patients was actually a success from a surgical standpoint but unfortunately died of a pulmonary infarction on the ninth postoperative day. Seybold,[40] Priviteri,[41] and Rigdon and Ellis [42] also reported on patients who had thoracotomy and died.

Other specific operative maneuvers which have been performed for this condition include superior mediastinotomy (this patient died 17 hours after onset),[43] posterior mediastinotomy and intercostal drainage (this patient died 43 hours after onset),[39] and abdominal approach for mediastinal drainage (this patient died 48 hours after onset).[25p]

It is our definite impression that any maneuver which is performed to drain either the mediastinum or the pleural cavity will increase or prolong the life of the patient. The number of patients whose survival period was increased or prolonged may not be statistically significant, but such statistics do indicate that duration of life is increased by as simple a procedure as thoracentesis. In 36 cases in which no specific therapy was given we were able to determine a definite duration of life. These patients, on an average, lived 18.4 hours after the onset of illness. The survival period varied from 2 to 48 hours. Certain cases by necessity had to be eliminated from this group, since in these cases the duration of life could not be definitely determined. There were three patients who had thoracenteses done only as a form of therapy, and these patients averaged 45 hours of life after onset. This varied from 15 to 96 hours. Patients who had thoracenteses and intercostal catheters numbered four. Their average duration of life was 104 hours, varying from 24 to 288 hours. Patients who had a thoracentesis followed by resection of a rib, with the thought of draining an empyema, numbered six. Their duration of life averaged 226 hours and ranged from 24 to 408 hours. We feel that this indicates a trend, namely, that any method of drainage of the pleural cavity or mediastinum will increase the patient's life. However, as mentioned before, examination of these figures reveals that they are not truly statistically significant. Perhaps the trend will be continued with report of future articles when the duration of life from onset to death can be more carefully stated.

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37. Clifton, E. E.: Spontaneous Rupture of Esophagus, Ann. Surg. **130**:1066 (Dec.) 1949.

38. Scholefield, J.: Spontaneous Perforation of Esophagus, Brit. M. J. **1**:348 (Feb.) 1949.

39. Ware, P. F., and Strieder, J. W.: Spontaneous Perforation of Normal Esophagus, Dis. Chest **16**:49 (July) 1949.

40. Seybold, W. D.; Johnson, M. A., III, and Leary, W. V.: Perforation of Esophagus, S. Clin. North America **30**:1155 (Aug.) 1950.

41. Priviteri, C. A., and Gay, B. B., Jr.: Spontaneous Rupture of Esophagus, Radiology **57**:48 (July) 1951, Case 4.

42. Rigdon, H. L., and Ellis, N. D.: Spontaneous Rupture of Esophagus, Dis. of Chest **19**:598 (May) 1951.

43. Charles, J. J.: Case of Rupture of Esophagus, Dublin Q. J. M. Sc. **1**:311 (Nov.) 1870.

10. *Unusual Aspects.*—Some of the unusual occurrences at the onset of the disease might be worth while to know and these are recorded in Table 6.[44]

REPORT OF A CASE

G. R., a 47-year-old Negro man, was admitted to Gallinger Municipal Hospital at 12:50 a. m., July 17, 1950, in acute distress from chest pain and dyspnea. He was a known alcoholic and had been drinking heavily for three days. Fourteen hours before admission, after drinking a cup of coffee, he suddenly had a desire to vomit, which he restrained momentarily with considerable effort. Immediately after the vomiting he had a sharp epigastric pain which radiated to the left upper quadrant and into the left lower chest. This pain steadily increased in intensity, and within two hours marked dyspnea developed. The pain became substernal and was described by the patient as being very severe.

There was a history of a mild "cold" for the past week and a chronic morning cough without any other respiratory symptoms.

The blood pressure was 90/60, pulse rate 128, respiration 40, and temperature 100.4 F. He appeared acutely ill, markedly dyspneic, and apprehensive. The trachea was shifted to the right. The heart and mediastinum were also displaced to the right. The right lung was clear; the left lung field was hyperresonant over the upper quarter, with decreased breath sounds and flatness

TABLE 6.—*Unusual Aspects Associated with Esophageal Rupture*

Sensation as though something burst [44a-b]	7
Onset after lifting weight [44i, j]	2
Onset while lying in bed [44k, l]	2
Onset while walking upstairs [24b]	1
Onset while walking [16]	1
Onset during sleep [44m]	1
Onset during meal [44n]	1
Sensick [44p]	1
Cardiac arrest (our case)	1
Sensation of impending death [44q]	1
Under hospital treatment for duodenal ulcer [23]	1
During childbirth [44s]	1

over the lower three-quarters. The heart was normal. There was no subcutaneous emphysema and no Hamman's sign. The abdomen showed voluntary rigidity and marked tenderness over the upper quadrants.

A chest x-ray revealed a left hydropneumothorax with mediastinal shift. Thoracentesis was done, and over 1,800 cc. of coffee-colored fluid was removed, which was guaiac-positive and had an odor of sour wine. This liquid contained 26,000 white blood cells (98% polymorphonuclear leucocytes) and 2,000 red blood cells per cubic millimeter. It gave an acid reaction, and a smear showed Gram-positive and Gram-negative cocci, Gram-positive rods, but no food particles. Cultures subsequently grew Staphylococcus aureus, Streptococcus hemolyticus, Neisseria catarrhalis, and a Gram-negative rod. The amylase value of the chest fluid was within normal range.

44. (*a*) Beal.[12a] (*b*) Charles.[43] (*c*) Dryden.[5] (*d*) Griffin, J.: Case of Rupture of Esophagus, Lancet **2**:337 (Sept.) 1869. (*e*) Harrison.[25q] (*f*) Patek, A. J.: Two Cases of Rupture of Esophagus, M. News Philadelphia **64**:516 (May) 1894. (*g*) Priviteri, C. A., and Gay, B. B., Jr.: Spontaneous Rupture of Esophagus, Radiology **57**:48 (July) 1951, Case 4. (*h*) Williams.[24] (*i*) Griffin, R. S.: Spontaneous Rupture of Esophagus, Pennsylvania M. J. **35**:639 (June) 1932. (*j*) Rolleston.[13] (*k*) Barrett.[3] (*l*) Kinsella.[16] (*m*) Christie.[2b] (*n*) Miller, G. I.: Unexplained Perforation of Esophagus in Girl 10 Years Old, Post Grad. New York **26**:312 (March) 1911. (*o*) Turner, J.: Spontaneous Rupture of Esophagus, Clin. Rep. Melbourn Hosp. **9**:57 (June) 1938. (*p*) Sheldon, L., Jr.: Report of Death from Rupture of Esophagus. U. S. Nav. M. Bull. **13**:529 (Sept.) 1919. (*q*) Gott, R., Jr.: Spontaneous Rupture of Esophagus, Am. J. Med. Sc. **186**:400 (Sept.) 1933, Case 1. (*r*) Thomson.[23] (*s*) Kennard, H. W. H.: Rupture of Esophagus During Childbirth, Brit. M. J. **1**:417 (Feb.) 1950.

Both methylene blue and penicillin (100,000 units) were instilled into the chest. The initial pressure on tapping this hydropneumothorax was +2 to +6. A chest x-ray after thoracentesis showed some fluid remaining at the base of the left lung and 60% collapse of the left lung, the mediastinum being almost normal in position. There was no mediastinal or subcutaneous emphysema.

Other laboratory studies at this time revealed a normal electrocardiogram, negative Kahn reaction, hemoglobin value of 13.7 gm. per 100 cc., hematocrit reading of 48, 5,200 white blood cells, and a normal urine.

The patient was given oxygen, penicillin (100,000 units every three hours), and sulfadiazine (2.5 gm. intravenously). All nourishment was withheld by mouth, and intravenous fluids were given.

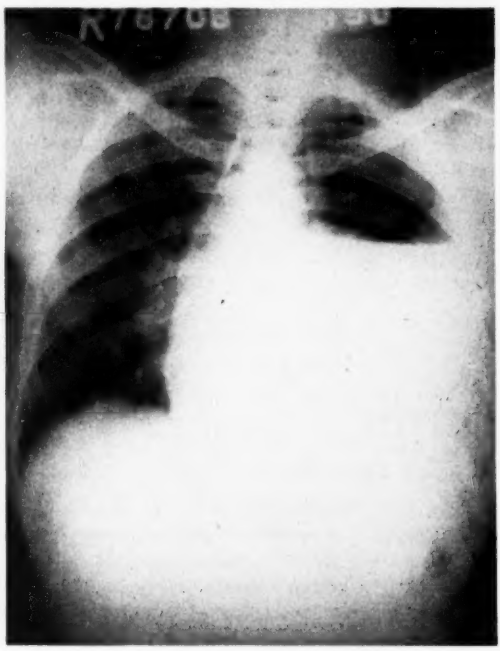

Fig. 1.—Roentgenogram taken on admission.

He was markedly improved after thoracentesis was done. However, within two hours after entry the blood pressure had dropped to 70/50, and the pulse rate was 120. Blood was started intravenously, and the blood pressure immediately responded.

The opinion at that time was that this patient's disease was due to (1) bronchopleural fistula, or (2) spontaneous rupture of the esophagus. The decision was made to operate on the patient with use of local anesthesia and with all preparations being made for a thoracotomy if such were necessary. This program was presented to the patient who stoutly refused any surgical intervention.

As a temporary procedure an intercostal catheter was placed in the eighth left interspace with the patient under local anesthesia. A Levine tube was placed in the stomach and Wangensteen suction drainage instituted. That same morning, nine hours after admission, there was a reaccumulation of fluid in the left hemithorax. The patient was markedly dyspneic.

At this time the patient agreed to surgery and accordingly was transferred to the surgical service. For operation (by G. W. W.) the patient was placed in the right lateral position, and

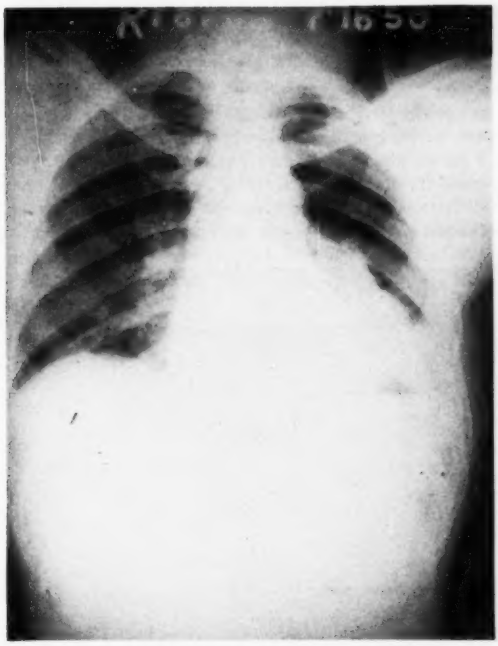

Fig. 2.—Roentgenogram taken after thoracentesis, with removal of 1,800 cc. of coffee-colored fluid. No mediastinal or subcutaneous emphysema was present.

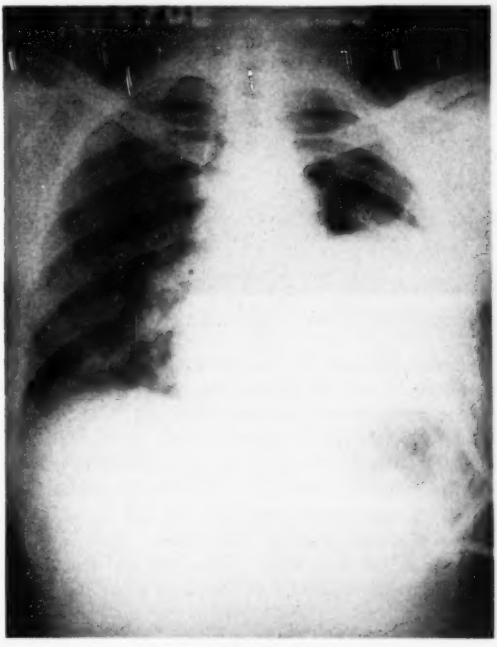

Fig. 3.—Roentgenogram taken just prior to surgery. Note intercostal catheter and lack of mediastinal or subcutaneous emphysema.

prepared and draped for an incision and drainage of an empyema. Complete setups were available for a full thoracotomy. The eighth rib was resected subperiosteally and when the periosteal bed was incised, it was immediately noticed that there was a free pleural space. Approximately 1 liter of dirty, reddish, purulent material was evacuated from the chest. Upon observation of the free pleural space the diagnosis of ruptured esophagus was obvious. Packs were placed into the wound and the anesthetist began administering general anesthesia (thiopental [pentothal®] sodium) immediately. Arrangements were somewhat hurried at this time and just prior to intubation apnea developed. According to the anesthetist this was approximately 30 seconds before the intratracheal tube was passed. Immediately after the intubation, the anesthetist told the surgeon of this finding, and the latter examined the heart through the operative wound

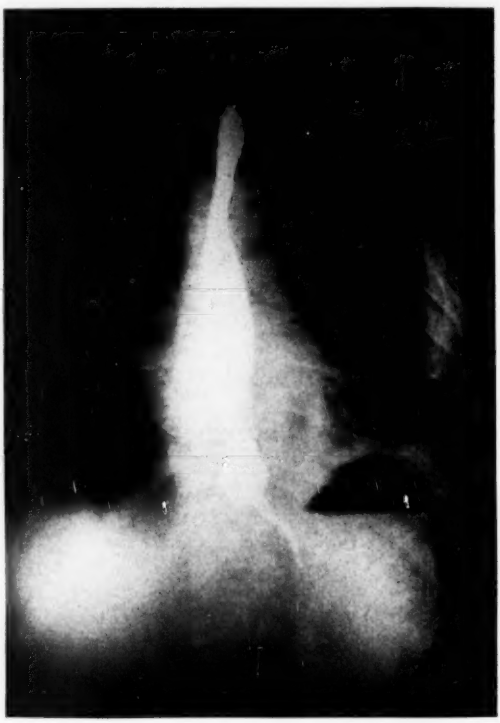

Fig. 4.—Roentgenogram taken 14 days after operation, showing stricture of esophagus.

and found that cardiac arrest had occurred. Cardiac massage by hand was begun; at the same time the wound was increased by an intercostal incision. The rib spreader was placed. The heart immediately responded to massage with a somewhat feeble beat. During this interval the thoracic aorta was compressed in order to increase the blood supply to the brain. The maximum period of cardiac arrest was approximately two minutes before a normal cardiac beat was established. The blood pressure rapidly rose to 90 systolic, and spontaneous respirations soon occurred.

The remainder of the rib was resected subperiosteally and the pleural cavity examined at leisure. The pleural surfaces showed an acute inflammatory reaction. An examination of the esophagus revealed an obvious rent in its lower portion that was 1 in. (2.5 cm.) in length and was on the left posterolateral surface about 2 in. (5.0 cm.) above the diaphragm. Palpation of the area did not reveal any evidence of esophageal ulceration. The edges were rather friable and showed an obvious local esophagitis. The mediastinum was split upward in order to insure

free drainage. The esophagus was closed in layers, with 000 chromic absorbable surgical (gut) suture material being used for the mucosa and two interrupted layers of black nonabsorbable surgical (silk) (000) sutures for the muscular layer. The final maneuver was that of suturing a flap of mediastinal pleura over the actual area of closure. The thoracic cavity was thoroughly irrigated with saline; streptomycin and penicillin were instilled and an intercostal tube placed in the ninth interspace. The incision was closed in layers, with use of a catgut technique. At the conclusion of the procedure the patient's pulse rate ranged between 120 and 140 and the blood pressure was 98/70.

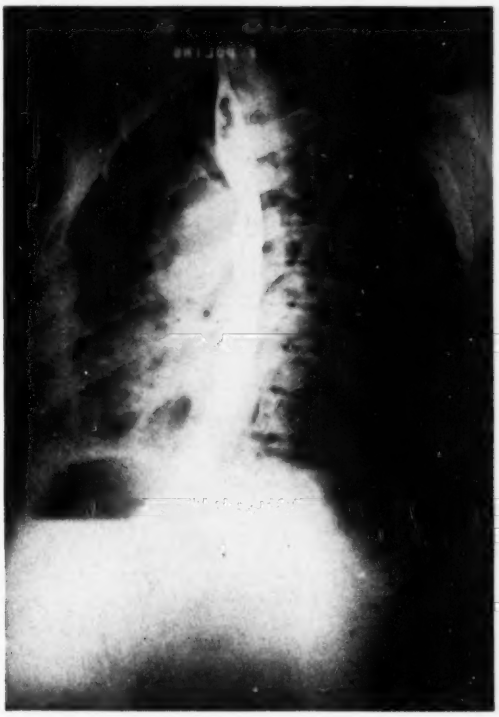

Fig. 5.—Roentgenogram taken 14 days after operation, showing stricture of esophagus.

The patient remained comatose during the afternoon and the early part of the evening. His blood pressure slowly rose during the day to 100/65, and his pulse rate averaged 120. The evening of surgery the patient was irrational and violent and had to be restrained.

The postoperative regimen consisted of continuing Wangensteen suction, giving blood transfusions, and administering streptomycin and penicillin. The day following surgery the temperature was 99 F., blood pressure 110/65, and pulse rate 110. On this day the patient was rational and able to answer questions intelligently but had a complete memory loss for the preceding day. Examination of the chest revealed many inspiratory rales on the left side; there was no abdominal pain.

The following day x-rays showed that the patient had loculated chest fluid; the intercostal tube was not functioning and was removed. Thoracentesis was done and approximately 50 cc. of fluid removed. Thoracenteses were performed for several days, and no more than 80 cc. of fluid were obtained at any time. Penicillin was instilled into the pleural cavity after each thoracentesis. Cultures of the fluid were made and yielded no organisms.

On July 20, the patient's temperature was 101.2 F., with a pulse rate of 100. On July 21, his temperature was normal; the patient appeared more ill, however, than at any time since surgery. He had numerous rales in the left chest, with dullness at the base of the left lung. A bronchoscopy was performed because it was felt that the lung had not expanded sufficiently. At the time of this procedure the left lower lobe orifice, although patent, showed a marked inflammatory reaction with a reddened friable mucosa, and considerable bronchial secretions were removed. After bronchoscopy the patient's condition immediately improved.

On July 27, 1950, it was felt that streptomycin was beyond the period of effectiveness and aureomycin was substituted. On this same day the Levine tube was removed and liquids by mouth started. The Levine tube had been left in the stomach for this long period lest reperforation occur. On succeeding days the patient partook of a liquid diet, a soft diet, and then a regular diet.

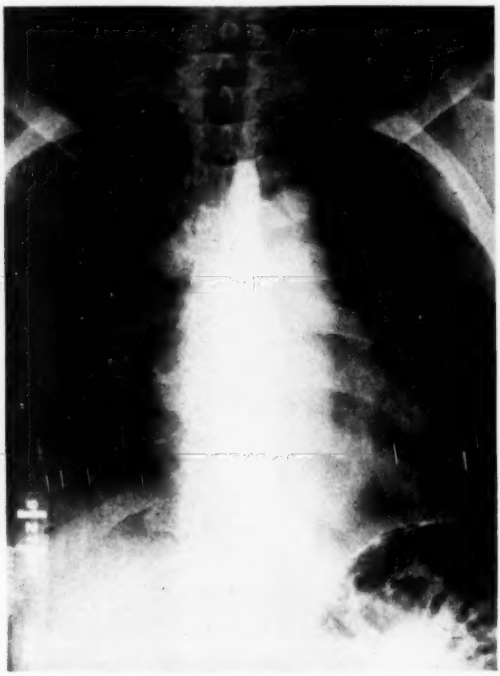

Fig. 6.—Roentgenogram showing result following dilatations.

On July 31, after a barium swallow moderate constriction of the lower third of the esophagus was shown. On Aug. 11, an electroencephalogram was done in order to attempt to detect any possible focal dysrhythmia following the period of cardiac arrest. The electroencephalogram was reported as normal.

Since a barium swallow showed constriction of the lower third of the esophagus, on Aug. 14, 1950, an esophagoscopy was performed. There was no evidence of mucosal ulceration. There was a sharp constricted area at 36 cm. from the incisor teeth, and this was gently dilated with soft dilators. Since the esophagus was rigid and it was rather difficult to manipulate the esophagoscope, a decision was made to do the dilations using a string as a guide. It was felt that this rigidity was due to the patient's previous infection and mediastinitis. From then on at regular intervals the esophagus was dilated over a string and dilations were continued, until finally on Sept. 1, 1950, a metal dilator, size 45, was passed with ease.

On Sept. 3, 1950, after a barium swallow the roentgenogram was reported as normal.

After the course of dilations the patient was discharged from the hospital. A repeat gastrointestinal series done October, 1950, showed no evidence of esophageal stricture or other pathological change. The patient at this time was completely asymptomatic and has remained so.

SUMMARY

A review of the English literature on spontaneous rupture of the esophagus is presented.[45] A total of 86 cases (including ours) fulfilling the criteria have been analyzed in detail. Seventy additional cases have been rejected as not fulfilling our criteria. Sixty-eight patients died; 18 survived.

The diagnosis should be suspected in every case with combined thoracic and abdominal findings. The commonest symptoms are epigastric pain and vomiting. The single most valuable laboratory test is the roentgenogram of the chest. Once the diagnosis is established or suspected the only definitive therapy is thoracotomy, all other measures being only palliative.

The differential diagnosis and proposed plan of treatment is discussed.

A case in which the diagnosis was made correctly and treatment with thoracotomy was successful is presented. Cardiac arrest, occurring while the patient was on the operating table, was a complicating factor in this case.

Dr. H. H. Hussey and Miss Neva Reese assisted in the preparation of this manuscript.

The Staff of the Library of the Surgeon General's Office, United States Army, assisted in compiling the bibliography.

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COMPARISON OF WOUND HEALING WITH AND WITHOUT DRESSINGS

Experimental Study

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IT IS NOT unusual, while making routine surgical rounds, to find that the dressing covering the inferior angle of an inguinal hernia wound has been dislodged, exposing this portion of the wound. About three years ago, one of us (C. J. H.) became curious about the healing of these exposed wound areas and noted that differences in wound healing between covered and uncovered areas were sometimes in favor of the uncovered portion.

Soon thereafter several inguinal hernia wounds were left completely uncovered except for the loose placement thereon of a sterile towel for an hour or two at the conclusion of the operation. These wounds healed as well as those having the customary dressings. Mengert and Hermes [1] in 1949 reported similar experiences in the handling of gynecological abdominal wounds. Before using this method more extensively, it seemed advisable to determine on experimental animals how quickly and effectively clean operative wounds with carefully approximated edges became sealed from external sources of bacterial contamination, and whether there were differences in healing between covered and uncovered wounds. DuMortier [2] stroked virulent cultures of Staphylococcus aureus hemolyticus along the line of closure of clean operative abdominal wounds of guinea pigs at various times during the postoperative period. He found that when this was done within the first six hours after closure the wounds almost invariably became infected. It was not until the fifth postoperative day that the wounds showed resistance to contamination comparable to that of intact skin. Since these wounds were kept covered by dressings during the duration of the experiment, conditions comparable to those of our proposed experiments, as described in Section 4 hereafter, did not exist.

From the Surgical Division of Homer G. Phillips Hospital and the Department of Surgery, Washington University School of Medicine.

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ANIMAL EXPERIMENTS AND RESULTS

1. *Incision and Closure.*—Young female rabbits were anesthetized with open drop ether and their abdomens were dry-shaved. The abdominal skin was prepared with ether, alcohol, and thiomersal (merthiolate®) tincture and the operative field draped with sterile towels. A vertical linear incision 2 cm. long was made in the midline and carried down usually by a single stroke through the full thickness of the skin and subcutaneous tissue. The bleeding vessels were ligated with 00000 braided silk. The wound edges were then carefully coaptated with interrupted sutures of 0000 braided silk.

2. *The Dressing.*—As controls in the wound healing experiment (Section 5) the wounds of alternate animals were covered with dressings. It was first necessary to devise a dressing which would remain on the animal throughout the length of the experiment and which would still approximate the type of dressing customarily employed on the human abdomen. After several failures, the following method of dressing the abdominal wound of the rabbit was successful. The wound was covered with three 3 by 3 in. (7.6 cm.) 12 ply, 20 by 12 mesh sterile gauze pads. The surrounding skin was painted with tincture of benzoin compound, which was allowed to dry. To maintain the gauze in position a piece of elastic adhesive tape, large enough to overlap the edges by 3 cm., was applied and the overlapping tape was firmly pressed to the coated skin. These dressings were found to stay in position for the 10 days that some of the experiments required.

3. *Wound Healing.*—Wounds were made and closed in four animals as described in Section 1. With the rabbit still under anesthesia, the entire wound was excised, together with a margin of normal skin and subcutaneous tissue, leaving the coaptating sutures intact. This operation was performed 15 minutes after closure in the first animal, 30 minutes in the second, 1 hour in the third, and 2 hours in the fourth. The blocks of tissue were fixed in formalin. Sections were made across the wound and stained with hematoxylin and eosin.

Microscopically, there was a progressive sealing of the space between the edges of the wound. The 15-minute section showed the deposition on the epithelial edges of fresh red blood cells, without visible fibrin. In the 30-minute section the clot filled the wound to its full depth and some fibrin was visible at the surface. In the one-hour wound fibrin deposition was noted throughout the wound and some dissolution of the red cells was present. After two hours there was more clot homogeneity, the red cells becoming further dissolved in a network of fibrin.

In general, these microscopic findings are comparable to those described in standard surgical textbooks. What interested us particularly, however, was how firmly the edges were glued soon after they were sutured together.

This observation was exemplified by experiments using the tensiometer described by Fast, Nelson, and Dennis [3] on five additional rabbits. Incision and closure were performed as described in Section 1. The wounds were not dressed. The sutures were removed just before the tensiometer was applied. The strength of the wounds was tested on the tensiometer immediately after closure (about five minutes after) in the first animal and after two hours in the second, four hours in the third, eight

3. Fast, J.; Nelson, C., and Dennis, C.: Rate of Gain in Strength in Sutured Abdominal Wounds, Surg., Gynec. & Obst. **84**:685, 1947.

hours in the fourth, and five days in the fifth. The results are expressed in grams pull of a calibrated spring needed to separate the edges of the wound.

5 minutes	30 gm.
2 hours	40 gm.
4 hours	40 gm.
8 hours	55 gm.
5 days	200 gm.

These experiments indicate that the coagulum of blood and fibrin which so early was visible between the edges of the wounds of the other rabbits also served to glue the wound edges. After five minutes it took a 30-gm. pull to separate them, and this pull was about half that needed to separate the edges after eight hours and about one-seventh that necessary after five days.

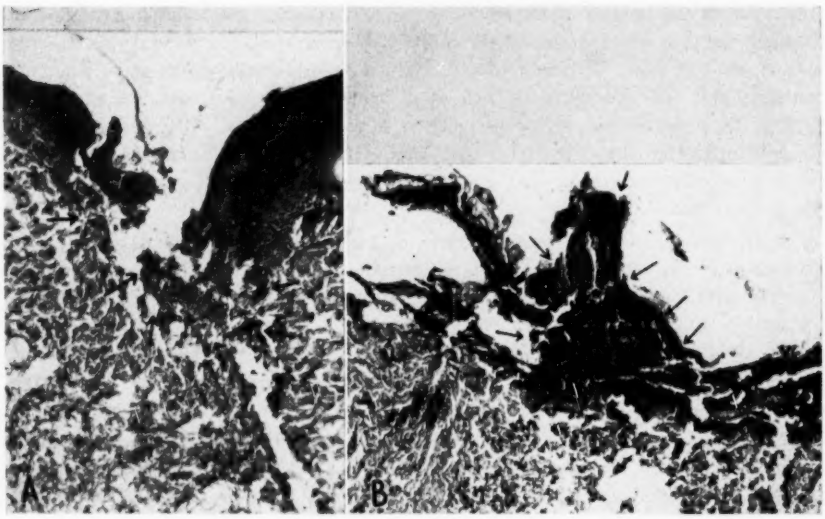

Fig. 1.—One day after wound closure. *A*, wound covered by dressing. A plug of disintegrating red blood cells and fibrin seals the wound. *B*, wound uncovered. The wound is covered by a coagulum of red blood cells and fibrin of greater thickness than in *A*.

4. *Bacterial Contamination.*—Wounds were made and closed on six animals in the manner described in Section 1. A heavy, pure culture of hemolytic Staph. aureus was stroked with moderate pressure on the wounds of these animals 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, and 8 hours after the wounds were closed. The wounds were left uncovered. Five days after the contamination, at a time when the tissue response to bacterial invasion should be pronounced, the wounds were excised in the manner described in Section 3. Microscopic sections were prepared and examined.

With the exception of the 30-minute wound, which showed some inflammatory reaction at the upper angle, all the wounds healed by primary union. Microscopically, healing had progressed in each instance to the stage expected on the fifth day. The section taken through the inflamed area of the 30-minute wound showed a small

subcutaneous abscess. Even if bacteriological studies could have been made on the pus of the abscess, it probably could not have been determined whether the infection resulted from the purposeful bacterial contamination or was an incidental wound infection. Since the other wounds, especially the 15-minute wound, did not become infected, it is likely that the infection of the 30-minute wound was fortuitous.

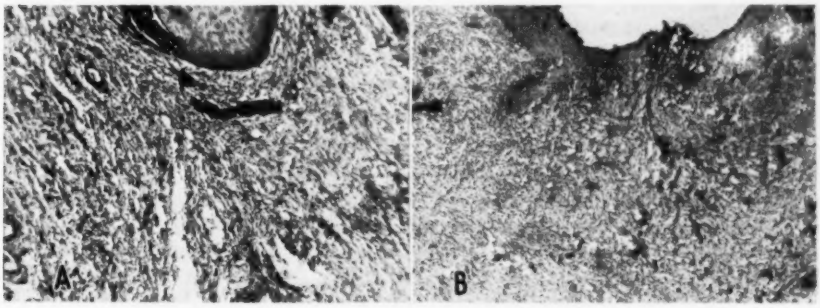

Fig. 2.—Six days after wound closure. The subepithelial layers of the dressed wound, *A*, and the uncovered wound, *B*, are healing equally well. Fibroblasts, round cells, phagocytes, and capillaries are present in both sections.

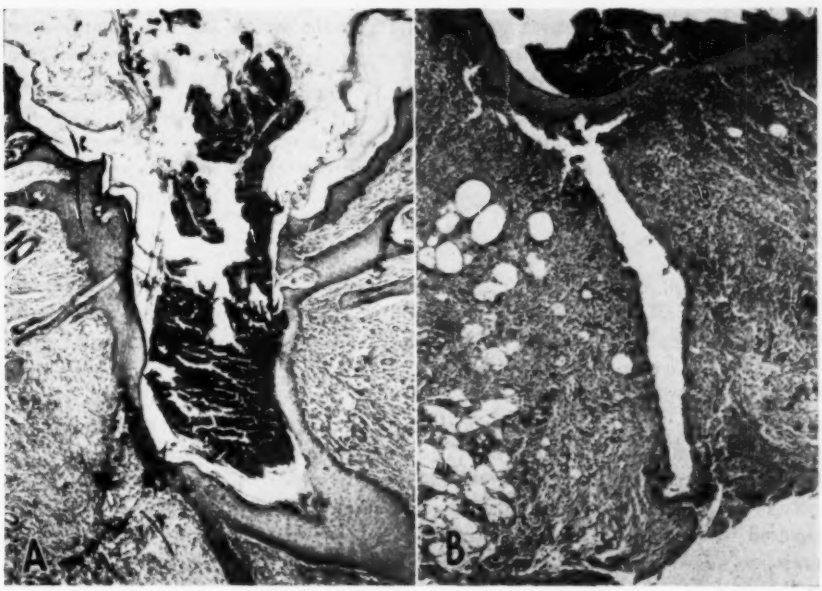

Fig. 3.—Eight days after wound closure. *A*, wound covered by dressing. Note the thick layer of epithelial debris over the healed epithelium. *B*, wound uncovered. Less epithelial proliferation and surface debris are present than in *A*.

These experiments indicate that as early as one hour after a clean incised wound is well coaptated, pathogenic bacteria can be allowed to come in contact with the wound without producing infection. It is even possible that contamination earlier than one hour after may be safe.

5. *Wound Healing.*—Wounds were made and closed in 12 animals as described in Section 1. The wounds of six animals were dressed as in Section 2; the wounds of the other six rabbits were left uncovered. On the 1st, 3d, 4th, 6th, 8th, and 10th days after surgery a pair of animals, one with a dressing and one without, were reanesthetized, their wounds were inspected, and block excisions of the skin and subcutaneous tissue around the wounds were performed in the manner described in Section 3. These wounds were sectioned and stained and were studied microscopically to compare the healing of the covered and uncovered wounds.

Macroscopically, the covered and uncovered wounds showed no appreciable differences until the fourth day after the operation. Starting with this day the covered wounds showed a tendency to become moist and encrusted. By comparison, the uncovered wounds continued to look dry and clean.

Microscopically, on the first day the covered and uncovered wounds were effectively sealed by a coagulum of fibrin and disintegrating red cells; the clot on the uncovered wound was thicker (Fig. 1). As the process of wound healing progressed, it was noted that the dermis and subcutaneous tissue healed with equal rapidity in the covered and uncovered wounds. By the sixth day the epithelium had grown across the surfaces, fibroblasts had proliferated across the deep layers of the wound, and capillaries were quite numerous (Fig. 2). It was noted, however, that after the third day there accumulated under the dressings a layer of cornified epidermis, disintegrated red cells, leucocytes, and bacteria. By the eighth day this accumulation had doubled the thickness of the epidermis (Fig. 3*A*). In contrast the uncovered wounds had very little surface debris (Fig. 3*B*).

A comparison of healing between wounds covered with dressings and those left uncovered shows no significant differences. The accumulation of surface debris under the dressings should probably be construed as prevention of desquamation by the dressings, and its presence cannot be considered to alter the repair of wounds.

COMMENT

The over-all experimental results lead us to conclude that in rabbits well-coaptated surgical wounds heal equally well through all the layers whether dressings are applied or not. Sealing and gluing of these wounds by a coagulum of fibrin and red cells occur within a matter of minutes. This gluing gives the wound considerable tensile strength even without the support of sutures, and the presence of sutures would seem to insure the maintenance of the seal against ordinary postoperative strain. The seal also seems to be an effective barrier against bacterial contamination from external sources, contrary to the findings of DuMortier. The significant difference between his and our experiments was the fact that his guinea pig wounds were covered by dressings and our rabbit wounds were not. Perhaps the absence of dressings allows quick drying of the surface coagulum, which gives earlier protection to the wound.

The question naturally arises, Is it necessary to cover the average surgical wound with a dressing? If the dressing is employed for protection from bacterial contamination and for its effect on wound healing, the answer would seem to be, No! Since dressings are also used for splinting, for their hemostatic effect, for keeping "dead spaces" closed, and for protection against trauma, it is obvious that many wounds still need them. Even so, some of these needs for dressings can be fulfilled

in the first 24 hours after surgery, after which the dressings may be removed. Since our experiments have shown that considerable epithelial debris accumulates under the dressings after the third day, keeping dressings on for a longer period may conceivably have an adverse effect.

If the routine application of dressings is not necessary, there are obvious advantages in leaving them off, such as the economy of surgical supplies, the saving of time and effort, the sparing of hospital personnel, the elimination of skin irritation from adhesive tape, and the chance to observe the wound more often.

On the basis of these animal experiments we are now conducting clinical studies at the Homer G. Phillips Hospital. Observations are being made on parallel series of clean surgical abdominal wounds with and without dressings, comparing the gross appearance, the surface bacterial counts, and the morbidity and the psychic reactions of the patients. Although these studies have not been completed, observations thus far indicate that wounds without dressings heal as well as similar wounds with dressings and that the patients in general do not object to our leaving the wounds uncovered. A detailed report of these experiments will soon be forthcoming.[4]

CONCLUSIONS

1. In the rabbit a well-coaptated surgical wound is rapidly sealed by a coagulum of red cells and fibrin. This early seal also give considerable tensile strength to the wound and prevents bacterial contamination from external sources.

2. In the rabbit well coaptated surgical wounds heal equally well whether uncovered or covered by dressings.

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STENOSING TENDOVAGINITIS OF THE DORSAL AND VOLAR COMPARTMENTS OF THE WRIST

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TENDOVAGINITIS is not tenosynovitis. The three primary causes of stenosing tendovaginitis are occupational stretching of the tendon, repeated active contraction of the muscle moving the tendon, and direct injury, the stenosis being the residuum of a gross blunt injury. Before there is stenosing tendovaginitis, there must be nonstenosing tendovaginitis. It takes time to make a sheath stenotic. The latter is reversible, the former is not.

I. STENOSING TENDOVAGINITIS OF THE FIRST DORSAL COMPARTMENT

De Quervain's disease is the stenosing tendovaginitis of the abductor pollicis longus and the extensor pollicis brevis tendons at the level of the styloid process of the radius.

The recent literature has emphasized the anatomical variations in the tendons of the first dorsal compartment and the clinical variations of stenosis influenced by the anatomical variations. Loomis [1] (1951) described five variations which may be reduced to two: 1. There is stenosis of one or both separately ensheathed tendons. Murphy [2] (1949) had previously described stenosis of the separately ensheathed extensor pollicis brevis. 2. There is stenosis of the aberrant tendon in its separate canal, with or without associated stenosis of the two tendons in the main osteofibrous canal. Loomis found a hidden stenotic tendon in the dorsal part of the first compartment nine times. This aberrant tendon may be the extensor pollicis brevis, the abductor pollicis longus being doubled. Fenton [3] (1950) had previously reported the volar position of the hidden tendon, the third tendon being found at the reoperation necessitated by persistence of disability.

I described a third variation, the separate stenosis of an aberrant tendon within the common sheath in 1951 [4] (Case 2). In none of these cases was the aberrant tendon excised to achieve cure, except in the cases of Bunnell.[5]

1. Loomis, L. K.: Variations of Stenosing Tenosynovitis at the Radial Styloid Process, J. Bone & Joint Surg. **33-A**:340, 1951.

2. Murphy, I. D.: An Unusual Form of de Quervain's Syndrome: Report of 2 Cases, J. Bone & Joint Surg. **31-A**:858, 1949.

3. Fenton, R.: Stenosing Tendovaginitis at the Radial Styloid Involving an Accessory Tendon Sheath, Bull. Hosp. Joint Dis. **11**:90, 1950.

4. Burman, M.: The Separate Stenosis of an Anomalous Extensor Tendon of Thumb in de Quervain's Disease, New York J. Med. **51**:2417, 1951.

5. Bunnell, S.: Surgery of the Hand, Philadelphia, J. B. Lippincott Company, 1944, pp. 332-339.

De Quervain's [6] disease is a common malady, especially of the needle trades, dominantly affecting women in their later middle years of life. The ordinary cause of stenosis is the occupational stretching of the tendons over the styloid process of the radius. Less common is direct injury. I have never seen an example of this stenosis by repeated active contraction of the abductor pollicis longus. In certain cases, de Quervain's disease, or a disease equivalent to it, is caused by primary tendinous rupture or anomaly (Shepherd [7]), by roughness of the tendon bed, or by malignant change of the tendon sheath (Wild [8]).

Stenosis is usually unilateral, but bilateral involvement, simultaneous or not, is seen. The oval swelling over the radial styloid is firm and sensitive to pressure. Forced adduction gives exquisite stretching pain (Finkelstein [9] sign). The thumb never triggers or locks. Abduction of the thumb is sometimes painful, and, since the abductor pollicis longus is a secondary supinator of the forearm, pronation, which stretches the muscle, gives pain. The grip is weakened and simple things, such as buttoning, are painfully done.

The diagnosis of de Quervain's disease is simple if one is aware of it. The radial styloiditis of Mouchet [10] (1933), a malady believed akin to epicondylitis or like strain of any bony prominence, shows symptoms and signs like those of de Quervain's disease. Emphasis is placed on the roentgenographic evidence of decalcification of the styloid process, thinning of its cortex, periostitis, and exostotic spicules. Cure follows prolonged conservative treatment or the curettage of the styloid process. None of the writers mention de Quervain's disease as the possible cause of the illness, except Praud [11] who curetted the styloid process in a typical case of de Quervain's disease.

The two sequelae to the operative resection of the sheath are scar incarceration, or neuroma, of the superficial branch of the radial nerve, and the not uncommon luxation of the tendons from their groove on volar flexion of the wrist and forward thrust of the thumb after too extensive resection of the sheath.

CASE 1.—*A maximal stenosis of the tendon sheath.*

A woman, 31 years old, had worked as a cashier and bookkeeper for 10 years. During this time she made countless movements which stretched the tendons of the first dorsal compartment. She typed and wrote all day and had to lift heavy ledgers. Her right wrist became painful and swollen in July, 1949, the severe pain waking her from her sleep. Her illness slowly worsened, and the pain radiated up the forearm and down to the tip of the thumb. The swelling over the styloid became larger and larger.

6. De Quervain, F.: Über ein Form von chronischer Tendovaginitis, Cor. Bl. schweiz. Aerzte **25**:389, 1895; Stenosierende Tendovaginitis am Handgelenk, ibid. **42**:355, 1912; Deutsche med. Wchnschr. **38**:736, 1912.

7. Shepherd, J. A.: Constriction of the Extensor Pollicis Brevis Tendon: An Unusual Lesion Simulating de Quervain's Disease, Brit. J. Surg. **34**:213, 1946.

8. Wild, quoted by Winterstein, O.: Über Sehnenscheidenstenosen, Ergebn. Chir. u. Orthop. **23**:151, 1930.

9. Finkelstein, H.: Stenosing Tendovaginitis at the Radial Styloid Process, J. Bone & Joint Surg. **12**:509, 1930.

10. Mouchet, A.: Styloïdite radiale chez un jouesse de tennis, Bull. et mém. Soc. nat. chir. **60**:351, 864, 1934; Rev. orthop. **20**:539, 1933.

11. Praud, F.: Contribution à l'étude de la ténosynovite sténosante de de Quervain, Thesis, Paris, Amédée LeGrand, 1939.

Examination revealed the typical features of de Quervain's disease, the most significant being the large firm spherical swelling over the radial styloid process. The mass was ½ in. (1.27 cm.) in diameter, the largest I have ever seen (Fig. 1). Roentgenograms of the wrist showed questionable decalcification of the styloid process and an enchondroma in the semilunar bone. At operation on Feb. 11, 1950, with use of general anesthesia and tourniquet control, the thick tendon sheath was exposed through a crease incision. The sheath was at least 3/16 in. (0.48 cm.) thick. The three tendons within the sheath seemed normal.

She was well on March 29, 1950, when treatment was stopped. A volar luxation of the abductor tendon took place on forward thrust of the thumb with the wrist volarly flexed.

CASE 2.—*De Quervain's disease associated with nonstenosing tendovaginitis of the insertion of the abductor pollicis longus.*

A woman, 59 years old, referred to me on July 28, 1950, complained of pain at the base of her left thumb, occupationally induced. She held stiff lace fabric with the thumb and index finger of her left hand as she sewed the material with the right hand. She did such work eight

Fig. 1.—Preoperative photograph (Feb. 10, 1950) illustrating maximal swelling of thickened tendon sheath of first dorsal compartment of right wrist. Left wrist is shown for comparison.

hours a day, two or three days each week. The pain, beginning in April, 1950, became so intense that she stopped work on May 5, 1950. She had been unrelieved by application of leeches, procaine injections, heat applications, and plaster immobilization of the thumb for 10 days.

The firm, tender, ball-like swelling over the styloid process of the radius and the induction of severe pain on adduction of the wrist with the thumb at the side of the hand made the diagnosis of stenosing tendovaginitis of the abductor pollicis longus and extensor pollicis brevis certain. On Aug. 14, 1950, the sheath was exposed through a crease incision ¾ in. (1.91 cm.) long, with the patient under general anesthesia and with the use of the pneumatic tourniquet to make the operative field bloodless. The sheath, thickened to more than 1/16 in. (0.16 cm.), was resected to expose the underlying tendons. An anomalous extensor brevis tendon, dorsally placed to its parent tendon, was separately ensheathed. Its stenotic sheath was resected. The postoperative course was uneventful. She returned to work near the end of September.

The radial styloid was slightly sensitive on March 21, 1952. A nontender swelling, found at the insertion of the abductor pollicis longus, was most evident on extension and abduction of the thumb. This unusual association was first noted on Nov. 24, 1950. (This case was reported in the *New York State Journal of Medicine*, Oct. 15, 1951.)

II. THE STENOSIS OF THE SECOND AND THIRD COMPARTMENTS

On the radial side of the dorsal, or Lister's,[12] tubercle lie the tendons of the extensor carpi radialis longus and the extensor carpi radialis brevis and on the medial side the tendon of the extensor pollicis longus. The two sheaths may be simultaneously but variably thickened, or there may be separate stenosis either of the sheath of the extensor carpi radialis tendons or of the sheath of the extensor pollicis longus. Each form of stenosing tendovaginitis has been described. Vischer[13] (1919) reported a case in which stenosis of the sheath of the extensor carpi radialis longus and the extensor carpi radialis brevis was associated with de Quervain's disease. Jagerink[14] (1928) operated on a young woman with a similar stenosing tendovaginitis. Winterstein[15] (1930) described the case of a young man whom he believed to have stenosing tendovaginitis of the extensor carpi radialis and extensor pollicis longus tendons at the level of the wrist. Pahl[16] (1932) reported on a woman, aged 62, treated nonoperatively, with probable stenosis of the sheath of the extensor carpi radialis. Lapidus and Fenton[17] (1952) reported a case of this stenosis, not operatively confirmed.

Stenosis of the sheath of the extensor pollicis longus is commoner than the stenosis of the radial extensors of the wrist. Winterstein[18] (1928) reported the first example of this malady in a girl 20 years old, who pressed strongly on the rotating ring of a polishing machine. A spindle-shaped thickening of the sheath of the left extensor pollicis longus, placed distally to the dorsal carpal ligament, was resected to effect cure. Pahl[16] (1932) reported cases of this stenosis in a woman aged 66 and in a man aged 20. Pohl[19] (1936) resected the sheath of this tendon in a woman, 60 years old, who had fallen on the left hand three months previously. Liavaag[20] (1945) treated a like stenosis operatively in a man aged 38. The fibrous sheaths of the second and fourth dorsal compartments were also thickened. Finkelstein[9] (1930) noted the simultaneous occurrence of stenosing tendovaginitis of the extensor pollicis longus and stenosing tendovaginitis of the abductor pollicis longus. In a second case, the stenosis of the sheath of the extensor pollicis longus was coincident with a ganglion connected with the wrist joint. Lapidus and Fenton[17] (1952),

12. Lister, J.: The Collected Papers of Joseph, Baron Lister, Oxford, The Clarendon Press, 1909, Vol. 2.

13. Vischer, A.: Beitrag zur Histologie der chronischer nicht tuberkulösen tendovaginitis, insbesondere auch der stenosierenden Form, Cor. Bl. schweiz. Aerzte **49**:103, 1919.

14. Jagerink, T. A.: Über zwei noch nicht beschriebene Formen von Tendovaginitis stenosans, Ztschr. orthop. chir. **50**:703, 1928; Über Styloidalgia radii en enkele andere gevallen von tendovaginitis stenosans, Nederl. tijdschr. geneesk. **72**:3228, 1928.

15. Winterstein, O.: Über Sehnenscheidenstenosen, Ergebn. Chir. u. Orthop. **23**:151, 1930.

16. Pahl, H.: Ein Beitrag zur Tendovaginitis stenosans de Quervain, Inaugural Dissertation, Hamburg, Buchdruckerei Thiele, Lippstadt- Westf., 1932.

17. Lapidus, P. W., and Fenton, R.: Stenosing Tendovaginitis at the Wrist and Forearm: A Report of 423 Cases in 369 Patients with 354 Operations, A. M. A. Arch. Surg. **64**:475, 1952.

18. Winterstein, O.: Über Sehnenscheidenstenosen am Handgelenk, Schweiz. med. Wchnschr. **58**:746, 1928.

19. Pohl, H.: Sehnenscheidenstenose des Musculus extensor pollicis longus sinister, Med. Klin. **32**:1596, 1936.

20. Liavaag, A. K.: Om stenoserende tendovaginitter, Nord. med. **28**:2617, 1945.

summarizing the 423 cases of stenosing tendovaginitis of the wrist seen at the Hospital for Joint Diseases, New York, found six cases of stenosing tendovaginitis of the extensor pollicis longus (1.4%) and two cases of stenosing tendovaginitis of the extensor carpi radialis (1%). One of these is my Case 4. I have seen at least 10 to 15 cases, in three of which the diagnosis was operatively confirmed.

There is variable pain over Lister's tubercle which may radiate proximally and distally. Tenderness is present over the tubercle, and sometimes a ball-like thickening is seen or felt there. The active or passive flexion of the distal phalanx of the thumb sometimes gives pain over Lister's tubercle, but the flexion and extension of the distal phalanx of the thumb is never blocked. The grip is weakened. The associated lesion is epicondylitis of the elbow by strain of the origin of the radial extensors of the wrist. Less often, there is strain of the shoulder. At operation there is found a stenosing or a nonstenosing tendovaginitis of the radial extensors of the wrist, a stenosing tendovaginitis of the extensor pollicis longus at its bend about the pulley of Lister's tubercle, and once I found a thickening of the radial part of the fibrous sheath of the common extensor tendons. The lesion is actively produced by contraction of the muscles in the unnatural antigravitational act of dorsiflexion and abduction. The likely cause is the occupational stretching of the tendons, the greater tension falling on the extensor pollicis longus.

CASE 3.—*The active form of this disease as a consequence of writer's cramp: Combined stenosis of the second and third compartments with associated epicondylitis.*

A man, 57 years old, seen on Jan. 19, 1948, had complained of pain in the dorsoradial part of his right wrist for three years. He is right-handed. He could not write well with this hand. He also complained of pain over the tip of his right shoulder and on the outer side of his right elbow. He had noted a lump over the wrist. A firm spherical swelling was found over Lister's tubercle, ¼ to ⅜ in. (0.64 to 1.06 cm.) in diameter. The wrist motions were free. In addition to the stenosing tendovaginitis of the radial extensor tendons of the wrist, he had epicondylitis of the right elbow and osteoarthritis of the right acromioclavicular joint.

A bloodless operation was done with use of tourniquet control and with the patient under general anesthesia on Jan. 27, 1948, through a longitudinal incision with the swelling at its midpart. A gelatinous fluid escaped from the opened sheaths. The fibrous sheath of the extensor pollicis longus was thickened, constricting the tendon, whose surface was rough and red. The sheath of the radial extensors was less thickened. The thickening of the fibrous coats of these tendons was greatest where they merged on Lister's tubercle. The thickened sheaths were split and resected. An accessory extensor tendon of the thumb was found on its ulnar side. The carpal ligament was loosely closed.

The wrist was freely movable on March 3, 1948. When it was placed in volar flexion and adduction, it slowly rose to dorsiflexion and abduction, in which position it was maintained. A slight cracking was felt over Lister's tubercle as the tip of the thumb was bent and straightened. The external epicondyle of the elbow was still tender. The operation had not helped him. His neurologic condition remained unchanged in May, 1952.

The genesis of this malady is the sustained position of the wrist in dorsiflexion and abduction in writing. It is a sort of writer's cramp, the sequel of which was this stenosing tendovaginitis. Relief can come only when the cramped position of the wrist is overcome. The surgical procedure is not enough.

CASE 4.—*The occupational form in which the affected extensor longus pollicis tendon is stretched around the pulley of Lister's tubercle.*

A woman, 40 years old, worked as a fountain girl. She scooped ice cream to make many hundreds of cones a day. The forearm supinated, and the index finger pressed against her scoop with force. She worked eight hours a day and had done this work for three years.

Her right wrist became painful in September, 1946. She still complained of fairly constant pain on Nov. 17, 1949, along the course of the right index finger, radiating to the wrist. The right hand felt weak.

Lister's tubercle was tender and a little swollen. The motions of the wrist were free, but volar flexion induced pain. The grip was weak. Flexion of the distal phalanx of the thumb did not provoke pain in the wrist. The diagnosis of tendovaginitis of the extensor carpi radialis longus and the extensor carpi radialis brevis, the extensor pollicis longus, and the extensors of the index finger was operatively confirmed on Dec. 3, 1949. The fibrous sheath of the radial extensors was not thickened, but its synovial sheath was both thickened and inflamed. The fibrous sheath of the extensor pollicis longus was thickened at the bend of the tendon. Its mucous sheath showed the same inflammatory response as the sheath of the radial extensors. The radial part of the sheath of the common extensor tendons was thickened and did not allow the passage of a probe. The thickened sheaths were excised. The operation relieved her of pain.

III. THE STENOSIS OF THE FOURTH DORSAL COMPARTMENT

Stenosis is found either ulnarly or radially at the maximal bend of the extensor tendons for the index and little fingers. The middle and ring fingers, pursuing a straighter course, escape stenosis.

Winterstein [15] (1930) reported two cases of combined stenosing tendovaginitis of the extensor indicis proprius and extensor digitorum communis, one of which was operatively verified. Lapidus and Fenton [17] listed one case of stenosing tendovaginitis of the extensor tendon of the index finger in their Chart I. An example of stenosis of the extensors of the index finger has been given in Case 4.

CASE 5.—*Occupational stenosing tendovaginitis of the second, third, and fourth compartments in which the middle finger is affected.*

A typist, 35 years old, complained of pain in her right middle finger on Dec. 6, 1949, which spread diffusely to the dorsum of the wrist. The movement of volar flexion in hitting the keys of her machine, the supination of the forearm after its pronation when the thumb hit the space bar, and active dorsiflexion of the wrist gave pain. She had a Colles' fracture of this wrist in 1943, with resultant restriction of volar flexion of the wrist, a movement which she may have thereafter forced.

A small, firm, very tender, spherical swelling about ⅜ in. in diameter, overlay Lister's tubercle. The swelling was easily seen on volar flexion of the wrist. This painful movement did not exceed 25 to 30 degrees and gave pain over the tubercle. Dorsiflexion of the wrist easily reached 90 degrees. She was given no treatment.

She was seen again on Dec. 13, 1951. The wrist was occasionally painful, and the use of certain household appliances, such as a vacuum cleaner, gave her pain and ache on the dorsoradial side of the wrist, with occasional radiation of pain into the index and middle fingers. The hand felt weak, although the right grip registered 40 lb. (18.1 kg.) on the dynamometer and the left 36 lb. (16.3 kg.). The ball-like swelling was unchanged.

The radiation of pain from the dorsal surface of the middle finger makes it likely that the extensor tendon of this finger was also involved and that she had a stenosing tendovaginitis of the second, third, and fourth compartments.

IV. THE STENOSING TENDOVAGINITIS OF THE FIFTH COMPARTMENT

Winterstein [18] (1928) reported the first case of stenosis of the sheath of the extensor digiti quinti proprius tendon, operatively confirmed, in a 19-year-old girl who sustained a direct trauma to the wrist. He reported this case as an example of stenosing tendovaginitis of the extensor carpi ulnaris tendon, but corrected his error when he published a second case in 1930.[15] Pahl [16] (1932) found stenosis of the fifth dorsal compartment in a girl of 11 years, with a prominent ulnar styloid after a fracture of the forearm two years previously.

I have operated on two patients with stenosing tendovaginitis of the fifth dorsal compartment, one of whom is reported on here. The other case is listed in Chart I of the paper by Lapidus and Fenton.[17]

CASE 6.—*Stenosing tendovaginitis of the fifth dorsal compartment and nonstenosing tendovaginitis of the fourth compartment.*

One of the many injuries a man 38 years old sustained in an automobile accident on July 14, 1951, was an injury of the left wrist. When I saw him on Oct. 8, 1951, he complained of pain in the wrist on sudden turning of the forearm. Motions of the wrist and forearm were free. There was tenderness over the fifth dorsal compartment and slight thickening of the tendon sheath just below the ulnar head. Lister's tubercle was tender. The tendon sheath of the fourth dorsal compartment was tender and thickened. A click was heard there as the wrist was moved.

A bloodless operation was done on Nov. 12, 1951, with use of general anesthesia. The dorsal carpal ligament of the fifth compartment was greatly thickened and did not allow the passage of the probe. After the ligament was split, the tendon of the extensor digiti quinti proprius was exposed. This, bound to the ligament and the ulnar head by fibrous tissue, was freed. A probe could be passed under the thickened dorsal ligament of the not yet stenotic fourth dorsal compartment. The underlying extensor tendons were normal. This sheath was loosely sutured, but the sheath of the fifth compartment was not.

The patient made an excellent recovery.

V. THE STENOSIS OF THE SIXTH DORSAL COMPARTMENT

Stein's [21] patient (1927) was a woman aged 43 in whom pain developed over the ulnar styloid process after a fall three years previously. The tip of the ulnar styloid was very sensitive and the soft tissues over it edematous. Operation revealed stenosis of the sheath of the extensor carpi ulnaris tendon. Finkelstein [9] (1930) included this case (his Case 4) in his series. She was well in the follow-up time of 14 months. Winterstein [15] (1930) reported the bilateral case of a woman, 59 years old, who made repeated turning movements of each forearm as she shaped and squeezed wet balls of paper, which she burned to heat her home. She recovered gradually after four months of treatment. Palmborg [22] (1949) reported one case, and Garsten [23] (1951) performed operations in three cases—in one of these the condition may have followed a fracture of the ulnar styloid a year before. Pahl [16] (1932) described the case of a presumably hysterical girl of 17 years in whom there was operative proof of the stenosis of the first and sixth dorsal compartments. Dickson and Luckey [24] (1948) described the operative findings in six cases of tenosynovitis of this tendon sheath.

CASE 7.—*Stenosing tendovaginitis of the flexor carpi radialis and extensor carpi ulnaris tendon sheaths after resection of the semilunar bone of the wrist*

The semilunar bone of the right wrist in a man aged 34 was removed by another surgeon on May 7, 1951, a month after the patient fell from a scaffold. Pain and weakness of the hand persisted and was localized to the tender and thickened sheaths of the extensor carpi ulnaris and flexor carpi radialis tendons. Supination provoked pain at the insertion of the latter tendon. At operation on March 15, 1952, these greatly thickened and adherent sheaths were resected, with prompt relief of pain.

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21. Stein, H. C.: Stenosing Tendovaginitis, Am. J. Surg. **3**:77, 1927.

22. Palmborg, G.: Om senskidestenonser i handleden, Svenska läk. **46**:2768, 1949.

23. Garsten, P.: Stenosis of the Extensor Carpi Ulnaris Tendon Sheath, Acta chir. scandinav. **101**:85, 1951.

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STENOSING TENDOVAGINITIS OF THE FLEXOR CARPI RADIALIS

Repetitive stretching movement in dorsiflexion and adduction is unnatural. The movement of volar flexion and abduction which contracts the tendon is easy. A likely cause of stenosis is direct injury.

Winterstein [15] (1930) reported a presumed case of this tendovaginitis, not confirmed by operation. Lipscomb [25] (1944) mentions tenosynovitis of the flexor carpi radialis tendon. I have operated on three patients with this stenosis; one was associated with trigger thumb and the other with a stenosing tendovaginitis of the extensor carpi ulnaris (Case 7).

CASE 8.—*Stenosing tendovaginitis of the flexor carpi radialis by direct injury.*

A tank cover, 6 in. (15.2 cm.) in diameter, fell on the dorsum of the left wrist and the region of the left index finger and thumb of a man, 28 years old, on July 8, 1949. On Nov. 2, 1950, another physician removed a ganglion, probably attached to the flexor carpi radialis tendon.

The patient still complained of pain near the most proximal part of the right thenar eminence on March 26, 1951, which radiated proximally along the volar side of the forearm. The motions of the wrist were free. The most distal part of the sheath of the flexor carpi radialis tendon was tender and thick. A small ganglion was attached to the radial side of this tendon above the stenotic sheath. Extension of the wrist gave pain. On Oct. 8, 1951, the tendon sheath of the

Fig. 2.—Preoperative photograph taken Dec. 3, 1951, showing ball-like swelling of sheath of flexor carpi radialis tendon near the tuberosity of the scaphoid bone.

flexor carpi radialis tendon was much more thickened than it had been. At operation on Dec. 4, 1951 (Fig. 2) the sheath of the flexor carpi radialis was found to be greatly thickened (¼ in.). The tendon was bound by fibrous tissue to the groove of the greater multangular bone in which it runs. The ball-like swelling, the supposed ganglion, arose from the superficial part of the sheath which had undergone mucinous degeneration. This was resected and the sheath split to restore full mobility to the incarcerated tendon.

The region of operation was a little tender in March, 1952. The patient returned to work three weeks after the operation.

COMMENT

There is now widespread recognition of the stenosing tendovaginitis of the first dorsal compartment, attested to by the many papers [26] not previously cited which have appeared since its initial recognition by de Quervain in 1895. It is important that the other localizations of the same malady be known.

114 E. 54th St.

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DIVERTICULITIS OF THE CECUM

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CECAL diverticulitis is a definite yet relatively infrequent clinical entity. In the differential diagnosis of pain in the right lower quadrant, the possibility of diverticulitis of the cecum is not often considered. From 1912, when the first case of diverticulitis of the cecum appeared to have been reported, to April of 1950, there had been only 118 reported cases. To this number the present authors are adding four cases.

The literature gives evidence of a belief that the delineation between the lower portion of the ascending colon and the upper part of the cecum is not well defined. Therefore, there is undoubtedly some incidence of diverticulitis of the ascending colon included in these reports on diverticulitis of the cecum. We have attempted in this paper to separate the former from true cecal diverticulitis.

A diverticulum, as defined by Dorland,[1] is a pouch or pocket leading off from a main cavity or tube. It may be true, if all layers are present, or false, if one, the muscularis, or more layers are absent. Diverticula may be congenital or acquired, and solitary or multiple. Cunningham [2] defines the cecum as a wide short cul-de-sac consisting of that portion of the large bowel below the valvula coli. Therefore, those lesions below this level are in the cecum. However, it is often difficult to differentiate between cecum and ascending colon during celiotomy, because of the inflammatory reaction and tissue distortion, particularly when the pathology is in the region of the ileocecal valve.

REVIEW OF LITERATURE

A review of the literature reveals that the first case of diverticulitis of the cecum appears to have been reported by Portier [3] in 1912.

Greensfelder and Hiller [4] reported two cases and stressed traumatic diverticula. The appendix had previously been removed in both of their cases. Burgess,[5] in his report of five cases, stated that there is less tendency toward nausea in diverticulitis

From the Department of Surgery of Mercy Hospital and Stritch School of Medicine of Loyola University.

1. Dorland, W. A. N.: American Illustrated Medical Dictionary, Ed. 22, Philadelphia, W. B. Saunders Company, 1951.

2. Cunningham, J.: Textbook of Anatomy, Ed. 5, New York, William Wood & Company, 1919.

3. Portier, F.: Diverticulite et appendicite, Bull. et mem. Soc. anat. Paris **37**:29-31, 1912.

4. Greensfelder, L. A., and Hiller, R. I.: Caecal Diverticulosis with Special Reference to Traumatic Diverticula, Surg., Gynec. & Obst. **48**:786-795, 1929.

5. Burgess, C. M.: Diverticulitis of the Cecum, Am. J. Surg. **50**:108-111, 1940.

of the cecum than in appendicitis. Jonas [6] was of the opinion that barium enema was contraindicated in the acute stage and that the simplest operative procedure was to be utilized. Baker and Carlile [7] noted that there might be an intussusception of the cecum and appendix into a large diverticulum. Busch and Friedfeld [8] stated that fecaliths were less likely to form in this region because of the liquid character of the feces, but if the neck of the diverticulum was narrower than its body the formation of the fecalith was furthered.

Noon and Schenk [9] stated that one of the commonest preoperative diagnoses in cases of cecal diverticulitis was appendicitis, and that at operation carcinoma was most frequently considered.

In 1947 Anderson [10] reviewed the literature and added eight cases from the Mayo Clinic. Some of those considered in that review were cases in which the diverticulum was located in the ascending colon.

Fairbank and Rob [11] believe that there is no pain in the diverticulum unless there is obstruction at its neck.

Mainetti, Mammoni, and Dorna [12] pointed out that a carcinoma can be roentgenologically differentiated from cecal diverticulitis by the presence of a triangular-shaped cecal wedge in the latter.

ETIOLOGY

The etiology of cecal diverticulitis has not been entirely established. Because of a multiplicity of factors there exist some major differences of opinion. It is our purpose here to enumerate what in our opinion are the more important etiological factors.

1. Retention of the residual form of the lateral appendix which is present in embryonic life and which usually disappears before the true appendix develops. The presence of diverticula on other areas of the cecum may offer some contrary evidence against this and may favor the acquired factor.

2. Enterogenous cysts, which are most frequent in the ileocecal region and usually medial in their location.

3. Hereditary factors, as reported by Graves [13] in a man and his daughter.

4. Eversion of a weakened area of the cecal wall resulting from an intraluminal rupture of an appendiceal stump or stump abscess.

5. Eversion of an area due to postoperative intraluminal migration of a purse-string suture.

6. Traction by intra-abdominal adhesions.

7. Traction on the appendices epiploicae, mesentery, or omentum with or without adhesions.

8. Weakening of the bowel wall at the site of vascular entry.

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6. Jonas, A., Jr.: Solitary Cecal Diverticulitis, J. A. M. A. **15**:194-197, 1940.

7. Baker, J. W., and Carlile, T. J.: Solitary Diverticulitis of the Cecum, J. A. M. A. **122**:354-356, 1943.

8. Busch, I., and Friedfeld, L.: Solitary Diverticulitis of the Cecum, Am. J. Surg. **57**:555-557, 1942.

9. Noon, Z. B., and Schenk, H. L.: Solitary Diverticulitis of the Cecum, Am. J. Surg. **68**:364-368, 1945.

10. Anderson, L.: Acute Diverticulitis of the Cecum, Surgery **22**:479-488, 1947.

11. Fairbank, T. J., and Rob, C. G.: Solitary Diverticulitis of the Cecum and Ascending Colon, Brit. J. Surg. **35**:105-107, 1947.

12. Mainetti, J. M.; Mammoni, O., and Dorna, R. I.: Diverticulitis solitaria del ciego, Día méd. **19**:222-228, 1947.

13. Graves, W. N.: Solitary Diverticulitis of the Cecum, Minnesota Med. **21**:615-617, 1938.

9. Inherent weakness of the bowel wall due to congenital factors, age, obesity, or atrophy of fat along the penetrating vessels.

10. Increased intraluminal pressure.

11. Trauma during intra-abdominal surgery.

12. Cathartics and purgatives.

Racial characteristics are not a strong contributing factor.

INCIDENCE

The incidence of diverticulitis of the large bowel is quite common. Ochsner and Bargen [14] report an incidence of 5.7% in 31,383 roentgenographic examinations of the colon. At the same time, 6.9% of the necropsies revealed the presence of colonic diverticula. Rankin and Brown [15] noted an incidence of 5.67% in 24,620 patients subjected to roentgenographic studies of the colon. Willard and Bockus [16] state that 1.5% of large bowel diverticula occur in the right half of the colon. The frequency of detectable inflammatory changes in these diverticula is difficult to determine. Ochsner and Bargen [14] are of the opinion that 14% become inflamed, whereas Rankin and Brown [15] give a figure of 17%. Of 700 cases of surgical diverticulitis of the colon, Anderson [10] stated that only 8 were located in the cecum.

AGE AND SEX

Cecal diverticulitis can occur at any age. The youngest patient, a 3-year-old girl, was reported on by Odqvist and Petrén [17] in 1931. This was an incidental finding at autopsy. Graves [13] and Gordon-Taylor,[18] on the other hand, each reported a case in a 69-year-old man, the maximum age represented in the literature. The incidence is comparatively evenly distributed between the ages of 20 and 69 years in the cases in which the age was stated. However, it appears more frequently during the third to sixth decades.

As to sex, the incidence of diverticula in the entire colon is twice as great in the male, a ratio of 2 to 1. In our experience, and as revealed in the literature, the incidence of cecal diverticula is almost evenly distributed between the sexes.

SYMPTOMS AND DIAGNOSIS

The symptoms and diagnosis of cecal diverticulitis are identical with those of acute appendicitis or one of its immediate complications. It is singular to note that in the entire literature on the subject, the preoperative diagnosis was correctly made in only three cases. In these instances a history of previous appendectomy and results of barium enema studies were significant. However, some discretion should be used in the consideration of barium enemas in the diagnosis of conditions

14. Ochsner, A. C., and Bargen, J. A.: Diverticulosis of the Large Intestines: An Evaluation of Historical and Personal Observations, Ann. Int. Med. **9**:282-296, 1935.

15. Rankin, F. W., and Brown, P. W.: Diverticulitis of the Colon, Surg., Gynec. & Obst. **50**:836-847, 1930.

16. Willard, J. H., and Bockus, J. L.: Clinical and Therapeutic Status of Cases of Colonic Diverticulosis Seen in Office Practice, Am. J. Digest. Dis. **3**:580-585, 1936.

17. Odqvist, B., and Petrén, T.: Ein Fall von angeborener Divertikelbildung des Blinddarms, Arch. path. Anat. **280**:581, 1931.

18. Gordon-Taylor, G.: Solitary Diverticulum of the Cecum, Proc. Roy. Soc. Med. **32**:896-897, 1939.

requiring abdominal surgery. The presence of a mass may appear to be clinically significant.

When the abdomen is opened, carcinoma of the cecum is often suspected. This is undoubtedly because of peridiverticular reaction and induration with involvement of the regional lymph nodes. In addition, a neoplasm of the cecum is commoner than cecal diverticulitis. Immediate microscopic examination of a section of frozen tissue may be desirable but not reliable unless tumor cells are identified.

It is interesting to note in cases of cecal diverticulitis that the appendix is frequently normal and often absent or minimally involved.

The differential diagnosis of cecal diverticulitis includes that of any right lower quadrant pathology.

TREATMENT

The treatment of cecal diverticulitis is essentially surgical, since acute appendicitis, as a rule, cannot be differentiated. General supportive measures, chemotherapy, antibiotics, gastrointestinal intubation, and sedation should be utilized as indicated.

The surgical approach to the abdomen is left to the discretion of the surgeon, inasmuch as the method is not significant. It is understood, however, that extensions of standard incisions are used in some cases to facilitate a more radical procedure.

The nature and extent of the surgical procedure used depends upon the magnitude of the pathology. The procedure may include drainage, excision, inversion, local resection, and radical resection.

COMPLICATIONS

Complications are frequent in this entity, the most common being fecal fistula. Next in order of frequency are wound infection, sinus tract formation, pneumonia, abdominal distention, and peritonitis. Gangrene of the bowel, thrombophlebitis, obstruction, abscess, and ventral hernia are uncommon. It is rather difficult to evaluate the incidence of rupture of the diverticulum. It appears, however, that this or its sequelae is not uncommon. Complications may occur without rupture, since inflammatory changes in the bowel wall may permit peritoneal contamination to occur. Gangrene of the cecum seems to appear more frequently in cecal diverticulitis than in appendicitis.

REPORT OF CASES

In the cases which we have observed, three patients were males and one a female. The preoperative diagnosis in two was acute appendicitis; in one subsiding appendicitis; and in the fourth, appendiceal abscess. An inversion and suture was carried out in two cases; a right hemicolectomy in the third, and diverticulectomy in the fourth case. In the third case it was most difficult to rule out a carcinoma of the cecum. There were no deaths, although in one case a small sinus developed. All the appendices were uninvolved. Barium enema examinations carried out in the late postoperative period failed to reveal the presence of other diverticula. The McBurney incision was used in two cases, one of which required an extension. In the other two right rectus incisions were used.

CASE 1.—The patient complained of sharp and constant periumbilical pain. This pain became more intense and localized in the right lower quadrant. There was no nausea or vomiting but

pain increased on ingestion of a small quantity of food. The significant physical findings were right lower quadrant tenderness with slight rigidity and positive psoas, Rovsing, and Blumberg signs. At the lateral aspect of the cecum a small mass was found at surgery. In the center of the mass was a solitary diverticulum which contained a fecalith and measured about 1 cm. in diameter. The appendix was essentially normal, but was removed after inversion of the diverticulum with a purse-string suture. Subsequent x-ray examination of the large bowel failed to reveal the presence of other diverticula.

CASE 2.—The patient gave a history of a dull aching pain in the right flank which radiated to the right lower quadrant and scrotum. The abdomen was obese and presented slight tenderness in the right lower quadrant. No masses were palpable. A diagnosis of subsiding appendicitis was made. At surgery the adipose tissue of the mesentery on the right side appeared edematous. An indurated, inflamed mass was discovered on the lateral wall of the cecum, which in some areas appeared necrotic. The retrocecal appendix was not inflamed, but was subsequently removed. A cecal mass with a lumen was removed, and the defect was repaired with chromic surgical suture reinforced with a purse-string suture. A follow-up barium enema examination

Fig. 1.—Gross specimen. Illustration shows opening of diverticulum (arrow) on the mucosa of the cecum, surrounded by smooth mucosa. The ileocecal valve is just below and to the right of the diverticulum. The ileum is to the right.

failed to demonstrate the presence of other diverticula. The pathologist reported no evidence of a muscular layer in the submitted specimen and hence this can be classified as a false diverticulum.

CASE 3.—The third patient complained of dull epigastric pain of 24 hours' duration. This pain became sharp, more intense, and radiated to the region of the anterior superior iliac spine. Vomiting did not occur, although nausea was present. There was right lower quadrant muscle splinting with exquisite tenderness, muscle spasm, and rebound tenderness. A questionable mass was palpated in this region. Rovsing's and Blumberg's signs were strongly positive. A diagnosis of acute suppurative appendicitis was made. At surgery a firm mass in the anterior medial region of the ileocecal junction was found, which involved the wall of the cecum and measured approximately 5 cm. in diameter. The appendix was not injected, but in its midportion was a small gray nodule. The regional nodes were firm and enlarged. A diagnosis of carcinoma was strongly suspected. A right hemicolectomy was carried out, with utilization of an end-to-end ileotransverse colostomy. The surgical specimen consisted of 24 cm. of large bowel and 17 cm. of terminal ileum. At the ileocecal junction was a moderately firm and lobulated mass involving the wall, which measured 6 cm. in diameter. On cut section the surface

was found to be granular and in one area trabeculated. There was a 4-mm. fecalith in the wall of the tumor, which revealed inflammation and necrosis. The appendix was 10 cm. long and 5 mm. in diameter. In its midportion was a small gray nodule which measured 2 mm. in diameter.

Microscopic diagnosis was as follows: (1) diverticulum of the cecum with an impacted fecalith and severe diverticulitis; (2) multiple peritoneal cysts of the appendix; (3) lymphoid hyperplasia and perilymphadenitis. Subsequent roentgenographic study of the colon showed no evidences of other diverticula.

CASE 4.[19]—This was a case of diffuse abdominal pain of 100 hours' duration, migrating to the right lower quadrant, but no other complaints except anorexia. The abdomen was flat,

Fig. 2.—Microscopic specimen. A small portion of mucosa of the cecum is shown at the upper edge of the section. The submucosa is markedly thickened and inflammatory. In the lower part of the section there is fatty tissue surrounded by inflammation. No muscularis is present between the mucosa and fibrofatty layer; therefore this is a false diverticulum; × 60.

and there was tenderness over McBurney's point, with rigidity in the right lower quadrant. A tender egg-sized mass was palpated in this region. Rectal digital examination revealed a suspected positive Wachenheim-Reder sign. The clinical impression at this time was a periappendiceal abscess. A mass was found at surgery, surrounded by omentum which was adherent to the lateral portion of the cecum. The omentum was dissected from the mass and the edematous cecum. A solitary diverticulum measuring ¼ in. (0.64 cm.) in diameter was noted. The

19. Drs. M. W. K. Byrne and J. M. Scheid gave permission to use this case report.

appendix was retrocecal and essentially normal. The diverticulum was removed and sutured with chromic surgical suture, which was followed with a silk purse-string suture. The appendix was then removed.

COMMENT

There are many reports in the literature on the presence of a fecalith in the diverticulum. It is believed that this contributes greatly to the initiation of inflammatory changes in the diverticulum. The true or false aspect, as determined microscopically, adds little to pathologic diagnosis, as symptoms and findings are as a rule similar in both. It is our impression that patients with acute cecal diverticulitis are not as toxic on admission as patients with acute suppurative appendicitis. It is interesting to speculate on the possibility that a true diverticulum may become false because of destruction of the muscular wall, due to inflammation with subsequent fibrosis. In most of the cases reported the diverticula were of the solitary type.

In our opinion, postoperative barium enema studies are of great importance in substantiating the preoperative diagnosis of cecal diverticulitis, either of the solitary or of the multiple type. If the lesion is solitary, the result of the studies will be negative; if multiple, the presence or absence of the diverticula will depend on the extent of the operative procedure.

Regarding the location of the diverticula, the commonest position noted in reports was lateral. The next most frequent site was medial. The relatively high occurrence rates in the lateral and medial walls of the cecum may be considered as factors in support of the congenital theory.

The prognosis of cecal diverticulitis is quite good. The over-all mortality from the first report in the literature, in 1912, to April of 1950, is 5.8%. This may on initial inspection appear to be quite high, but the greatest number of these deaths occurred before the clinical use of chemotherapeutic agents and antibiotics.

The marked decrease in the mortality rate in the more recent reports is undoubtedly attributable in great measure to antibiotics and chemotherapy, as well as to improved surgical technics, anesthesia, and pre- and post-operative care.

SUMMARY

1. The literature from 1912 to April of 1950 reveals 118 reported cases of diverticulitis of the cecum, to which we have added four cases.

2. Because the symptoms are identical, the condition cannot be differentiated clinically from acute appendicitis. Therefore, it is encountered only at operation.

3. At time of surgery, carcinoma is often difficult to differentiate from cecal diverticulitis.

4. The diverticula, usually solitary, are located most frequently on the lateral or medial side of the cecum.

EFFECT OF HYALURONIDASE ON RATE OF ABSORPTION OF SUBCUTANEOUS FLUIDS

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HYALURONIDASE has been shown to increase the rate of spread of fluid injected into subcutaneous tissues,[1] and thereby accelerate absorption of such fluids. Its action depends on the lysis of hyaluronic acid, the cementing agent in the intercellular ground substance, so that more surface area of cellular membrane is made available for equilibration and absorption. However, no quantitative studies have been reported on the effect of hyaluronidase under conditions of clinical use. I have already studied the apparent absorption rates of solutions commonly used for subcutaneous injection in clinical practice [2] which have served as controls for the present studies, designed to determine the effect of hyaluronidase, utilizing the same clinical technique.

METHODS

Isotonic (0.9%) sodium chloride solution and 5% glucose in water were injected subcutaneously in the thighs of eight patients who were in good clinical condition and who showed no evidence of dehydration or electrolyte imbalance. The thighs were marked and the circumference measured at three levels. Into one thigh 500 cc. of isotonic saline with 1 cc. of hyaluronidase (150 units) was injected subcutaneously, while, simultaneously, 500 cc. of 5% glucose in water with the same amount of hyaluronidase was injected into the opposite thigh. The hyaluronidase was injected into the tubing immediately after the infusion had been started. The fluids were administered in less than one hour in each case, and measurements of the circumference at each of the three levels were repeated at frequent intervals. It was assumed that the minimal time of absorption is that required for the leg to return to its preinfusion size.

FINDINGS

The averages of the results are depicted in the Chart. Each point represents the average increment in the thigh measurements of all patients. The Table reveals the marked individual variation, as four of the patients' thigh measurements returned to normal within 8 hours after the injection of saline, two after 10 hours, and two after 12 hours, but the over-all slope depicted in the Chart is delayed by the data for the last two. Striking variation was also noted after the injection of 5% dextrose

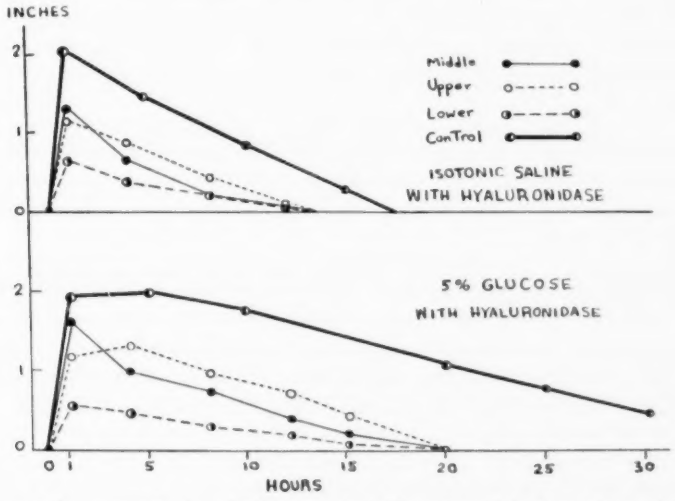
From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital.

1. Duran-Reynals, F.: The Effect of Extracts of Certain Organs from Normal and Immunized Animals on the Infecting Power of Vaccine Virus, J. Exper. Med. **50**:327, 1929. McClean, D.: The Influence of Testicular Extract on Dermal Permeability and the Response to Vaccine Virus, J. Path. Bact. **33**:1045, 1930.

2. Webb, W. R.; Lemmer, R. A., and Elman, R.: Absorption Rates, Electrolyte and Volume Changes Following Subcutaneous and Intraperitoneal Injections of Solutions Containing Salt, Glucose and Amino Acids, Surg., Gynec. & Obst. **91**:265, 1950.

in water, but in each patient saline was absorbed much faster than dextrose. It is evident that the thigh increments are far less in the patients receiving hyaluronidase than in the control group, a reflection of the increased diffusion rate occasioned by its use. Thus the time required for absorption of the 5% dextrose in water was reduced from over 30 hours to about 15 hours. Isotonic saline solution was absorbed in most patients in 7 to 10 hours, as compared with more than 15 hours in the control series. Thus under the clinical conditions observed here, the hyaluronidase has a maximal effect of doubling the rate of absorption of subcutaneous fluids.

Earlier, an attempt was made to make a more exact quantitative study by observing the effect of hyaluronidase on the fluid absorption from the peritoneal cavity of guinea pigs. It was found, however, that hyaluronidase does not increase the rate of absorption from the peritoneal cavity. This probably should have been anticipated, since the available membranous surface of a serous cavity is constant, while the



Average increments in size of thigh following subcutaneous injections of isotonic saline and 5% dextrose solutions, with and without hyaluronidase. The control curve shows the disappearance rate of the same fluids without hyaluronidase. Effect of hyaluronidase on the disappearance of subcutaneously injected fluids. Curve adapted from Webb, Lemmer, and Elman,[2] by permission of *Surgery, Gynecology & Obstetrics.*

available surface area of the subcutaneous tissues is almost unlimited. These observations confirm those of Banks, Seligman, and Fine, who found that hyaluronidase did not increase the rate of absorption of radioactive iodoplasma proteins administered intraperitoneally.

COMMENT

Hyaluronidase is a mucolytic enzyme[3] which acts on and depolymerizes the mucopolysaccharide, hyaluronic acid, which is the gel present in the ground substance of connective tissue. It is this gel which acts as a barrier to the free intercellular diffusion of fluid. It was early suggested that the clinical use of such a

3. Chain, E., and Duthie, E. S.: Identity of Hyaluronidase and Spreading Factor, Brit. J. Exper. Path. **21**:324, 1940.

spreading factor would facilitate the absorption of injected fluids by increasing the available cellular membrane and the number of available absorptive channels (capillaries and lymphatics).

A number of investigators [4] demonstrated a 5- to 14-fold increase in the rapidity of disappearance of localized intracutaneous and subcutaneous swellings produced by injections of both large and small volumes of fluid. They assumed, however, that this demonstrated an increased rate of absorption, rather than merely the increased rate of diffusion.

McClean and Morgan,[5] in one of the early studies, noted that the addition of testicular extract (hyaluronidase) to diphtheria antitoxin administered subcutaneously "approximately doubles the concentration of antitoxin in the blood at two and at six hours after its injection." Simon and Narins[6] found the mean time of disappearance of sodium iodomethamate (neo-iopax®) from control sites to be 113 minutes, while the mean time of disappearance when hyaluronidase was used was 79 minutes. Banks and co-workers [7] found the rate of absorption of radioactive plasma proteins injected subcutaneously in dogs to be increased from 1½- to 3-fold by the administration of hyaluronidase. The greatest difference was noted early in

*Time Required for Legs to Return to Normal Size**

	Less Than 8 Hr.	8-12 Hr.	12-15 Hr.	15-20 Hr.	More Than 20 Hr.
No. of pt. (5% glucose)	0	1	3	3	1
No. of pt. (isotonic saline)	4	2	2	0	0

* In both groups hyaluronidase was added. Note that isotonic saline solution disappears more rapidly than dextrose, although both do so much more rapidly than in similar experiments without use of hyaluronidase, as shown in the Chart.

the experiment, but the effect persisted to a lower degree over the eight-day duration of the experiment. It is interesting that even with hyaluronidase it required five days for 90% of the plasma protein to be absorbed. Pressure alone slightly hastened the absorption but was not comparable to the use of hyaluronidase.

Forbes and co-workers,[8] using very small amounts of radioactive sodium in isotonic saline solution, demonstrated an increased rate of disappearance of sodium from subcutaneous tissues. The rate was found to be extremely variable from one subject to another, but the addition of hyaluronidase in any given case always

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7. Banks, H. H.; Seligman, A. M., and Fine, J.: The Effect of Hyaluronidase on the Absorption of Parenterally Administered Radioactive Plasma Proteins in the Dog, J. Clin. Invest. **28**:548, 1949.

8. Forbes, G. B.; Deisher, R. W.; Perley, A. M., and Hartmann, A. F.: Effect of Hyaluronidase on the Subcutaneous Absorption of Electrolytes in Humans, Science **111**:177, 1950.

increased the rate of disappearance of the Na^{24} from the injection site. The appearance of the subcutaneously injected Na^{24} in the serum was likewise much more rapid with the use of hyaluronidase, and again the rate can be estimated to be approximately doubled. Despite individual variations, these many diverse studies using objective measurements have been amazingly consistent in showing over-all increase 1½ to 3 times in the rate of absorption of subcutaneous injections.

It is important to know whether absorption is in fact increased. The results observed here could be produced by diffusion alone, though the lack of demonstrable edema over the lower legs and abdomen suggests that the diffusion was not so extremely widespread as to be the major factor. The work of Forbes and others has shown that saline does enter the circulation more rapidly when injected with hyaluronidase. Since the large plasma protein and diphtheria antitoxin molecules likewise have been shown to enter the blood stream faster in the presence of hyaluronidase, it is a logical assumption that the glucose molecule also could be absorbed faster. However, the present study is not conclusive on this point and can be considered quantitative only in a negative sense—that the absorption time cannot be less than the interval required for the legs to return to their preinjection size.

Similarly, it is important to know if subcutaneous fluids in the presence of hyaluronidase must achieve equilibrium with the extracellular fluid of the body before being absorbed. While this point is not definitely clarified by the above studies, one can hardly believe the basic characteristics of semipermeable membranes would be altered, especially since the only known effect of hyaluronidase is to increase the available surface area of the semipermeable membrane. This is supported by the slower absorption and the greater increments of the size of the extremities following injection of 5% dextrose in water as compared with isotonic saline, which has a composition more like that of the extracellular fluid. Dextrose is slowly absorbed, and electrolytes from the body rapidly enter the solution to achieve equal electrolyte concentrations on both sides of the membrane. Thus the subcutaneous pool acts as if hypertonic and increases its volume at the expense of the extracellular fluid until the dextrose is completely absorbed. Studies are now in progress to further demonstrate this phenomenon in the presence of hyaluronidase.

The dangers of the use of nonelectrolyte solutions subcutaneously in dehydrated or sodium-depleted patients have been described in detail previously.[9] It is believed that the more rapid, temporary depletion of the extracellular fluid occurring in the presence of hyaluronidase increases these dangers and imposes on the clinician the need for greater precaution in its use.

SUMMARY

Despite very marked individual variation, hyaluronidase, used in eight patients, was found to double the disappearance rate of subcutaneously injected fluids.

With administration of hyaluronidase, 500 cc. of isotonic sodium chloride solution given subcutaneously disappeared as early as 8 hours, while a similar amount of 5% dextrose in water required about 15 hours, as compared with previously observed times of approximately 15 and 30 hours, respectively, without use of hyaluronidase.

9. Danowski, T. S.; Winkler, A. W., and Elkinton, J. R.: Biochemical and Hemodynamic Changes Following the Subcutaneous Injection of Glucose Solution, J. Clin. Invest. **26**:887, 1947. Webb.[2]

EFFECT OF ACTH, CORTISONE, AND DOCA* ON SURVIVAL OF BURNED RAT

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SEVERE burns are often fatal in both man and the experimental animal, despite adequate replacement of blood volume and electrolytes, the use of oxygen and antibiotics, and supportive therapy, including feeding, sedation, and early skin grafting. The role of the adrenal gland in burn mortality has been speculated upon extensively. Since the work of Selye [1] it has been well known that after a stress situation the adrenal gland becomes depleted of cholesterol and ascorbic acid and subsequently, in a matter of a few hours, exhibits a marked hyperplasia, as if an augmented production of cortical hormones was an important protective mechanism. Indeed, it has been shown that adrenocortical extract and cortisone enable the adrenalectomized animal to withstand certain stresses, i. e., work,[2] cold,[3] and typhoid vaccine.[4] The intact animal, however, is not protected by cortisone against the stress of limb ligation or radiation (Ingle [5] and Straube and associates [6]). The data concerning the use of adrenocortical extracts in the burn stress have been conflict-

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The supplies of corticotropin used in this research were generously supplied by Dr. Lawrence L. Lachat of Armour and Company, Chicago.

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6. Straube, R. L.; Patt, H. M.; Tyree, E. B., and Smith, D. E.: Influence of Level of Adrenal Cortical Steroids on Sensitivity of Mice to X-Irradiation, Proc. Soc. Exper. Biol. & Med. **71**:539-541, 1949.

ing.[7] You and Sellers [8] reported, in 1950, that adrenocortical extract given before burning failed to protect the adrenalectomized rat and that variable results were obtained when the adrenal extract was given after burning. Desoxycorticosterone (DOCA®) acetate given prior to burning protected both the adrenalectomized and the intact rat. Crassweller, Farmer, and Franks [9] have reported that the mortality from a severe burn in the mouse can be markedly reduced by treatment with a urinary extract containing a cortisone-like substance. Other workers have reported that neither adrenocortical extracts nor extracts of the posterior pituitary gland influence the burn mortality in the dog.[10] More recently, the postburn state in man has been likened clinically to an adrenal insufficiency state, and surgeons have advocated the use of cortisone and/or corticotropin (ACTH; adrenocorticotropic hormone),[11] in the treatment of severe burns (as well as in the treatment of other surgical traumata). Whitelaw [12] has been a strong advocate of the role of corticotropin in the promotion of healing following burns, and we must confess that, in seeing a small series of burn patients in a large naval hospital in Japan, we were impressed that in burn patients who received cortisone prompt drying of the wounds and rapid epithelization occurred. To us it seemed that the patient receiving cortisone did much better clinically than the patient who received no cortisone. Because of these conflicting evidences we have attempted to evaluate the role of corticotropin, cortisone, and desoxycorticosterone acetate in the treatment of an experimental burn in the laboratory.

METHOD

The experimental method was essentially that of You and Sellers.[8] White male rats of the Holtzman-Rolfsmeyer strain weighing approximately 150 to 170 gm. were used. The animals were maintained on standard Rockland farm rat diet, given water ad libitum, and housed in individual cages after burning. The rats were anesthetized by placing them in large bell jars over ether. The anesthetized rat was held by the feet and the clipped back immersed from the base of the neck to the base of the tail in a water bath of 85 C. for 30 seconds. Repeated measurement

7. Ingle, D. J., and Kuizenga, M. H.: The Survival of Non-Adrenalectomized Rats on Burn Shock With and Without Adrenal Cortical Hormone Treatment, Am. J. Physiol. **145**:203-205, 1945. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in Treatment of Fluid Shift in Severe Burns, Ann. Surg. **112**:150-157, 1940. Rhoads, J. E.; Wolff, W. A.; Saltonstall, H., and Lee, W. E.: Further Experiences with the Use of Adrenal Cortical Extract in Burn Shock, Ann. Surg. **118**:982-987, 1943.

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9. Crassweller, P. O.; Farmer, A. W., and Franks, W. R.: Experimental Burn Studies: Including Treatment with Cortisone-Active Material Extracted from Urine, Brit. M. J. **2**:242-245, 1950.

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12. Whitelaw, M. J., and Woodman, T. W.: The Treatment of Severe Burns with ACTH, J. Clin. Endocrinol. **10**:1171, 1950.

of the surfaces so burned indicated an average area of 30% of the body surface. The animals were given food and water and observed for 72 hours. We were interested only in the early burn mortality, i. e., that occurring during the first 72 hours, and no antibiotics were given. This particular experimental burn was chosen because it could be done with laboratory equipment immediately available and was relatively inexpensive of both time and material. However, we soon noticed that the mortality from this burn varied from experiment to experiment. The differences were attributed to variations in temperature (some of the experiments were carried on in summer heat), humidity, and so forth. Hence, each treated animal was controlled with an animal burned at the same time and was given either no treatment or isotonic sodium chloride solution, and each experimental group is reported with its own control. Rosenthal and Tabor, in 1945, demonstrated [13] unequivocally the marked protective effect of isotonic sodium chloride solution given subcutaneously to mice at the time of burning. In the following experiments we have confirmed this

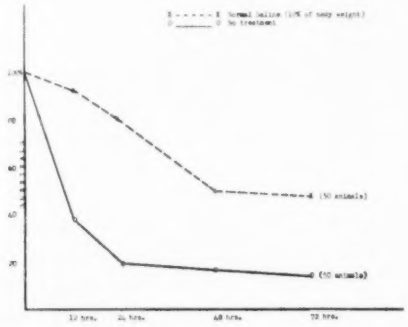

Chart 1.—Effect of treatment with isotonic sodium chloride solution on burn mortality.

finding in the rat and in some of the groups have compared the effect of treatment with that of treatment with isotonic sodium chloride solution given subcutaneously at the time of burning in amounts equal to 10% of body weight. Pathological studies were not done, and we report only the mortality curves and the 72-hour survival rates.

RESULTS

Experiment 1 demonstrates the effect of treatment with isotonic sodium chloride solution on the burn mortality in the rat. Alternate animals were given subcutaneously, immediately subsequent to the time of burning, isotonic sodium chloride solution in amounts equal to 10% of the animal's body weight. Chart 1 illustrates the ensuing mortality curve. In Experiment 2 one-half of the burned animals received no treatment, and the other animals were given 5 mg. of cortisone each 24 hours, the first dose being given immediately after burning. Chart 2 *A* illustrates the almost identical survival curves. In Experiment 3 all the burned animals

13. Rosenthal, S. M., and Tabor, H.: Electrolyte Changes and Chemotherapy in Experimental Burn and Traumatic Shock and Hemorrhage, Arch. Surg **51**:244-252, 1945.

received subcutaneously, at the time of burning, isotonic sodium chloride solution in amounts equal to 10% of body weight. Alternate animals received a single 5-mg. dose of cortisone given subcutaneously at the time of burning. The survival curves of these two groups were alike, as is shown in Chart 2 *B*. Chart 3 *A* illustrates the effect of pretreatment with cortisone. One-half of the animals were given, each 24 hours for four doses, 5 mg. of cortisone subcutaneously. After the last injection the animals were burned. At the same time an equal number of animals were burned and given no treatment. It is noted from Chart 3 *A* that none of the animals pretreated with cortisone survived more than 24 hours. This same experiment was

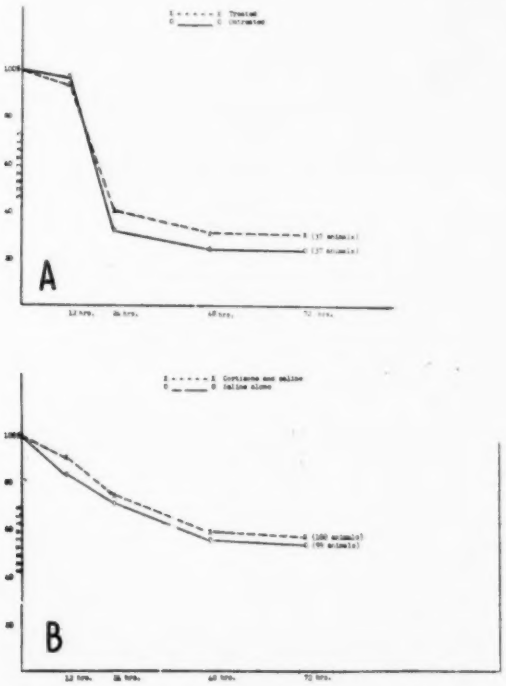

Chart 2.—*A*, effect of treatment with cortisone (5 mg. daily) on mortality of untreated burned rats. *B*, effect of treatment with cortisone (5 mg., single dose) on mortality of rats treated with isotonic sodium chloride solution (10% body weight).

repeated, except that now each burned animal received isotonic sodium chloride solution at the time of burning in amounts equal to 10% of body weight. Again, as shown in Chart 3 *B*, none of the animals which had been pretreated with cortisone survived more than 24 hours. In Experiment 6 all animals received isotonic sodium chloride solution at the time of burning. In addition, one-half of the animals received a 2.5-mg. dose of cortisone 12 hours before burning and again at the time of burning. This experiment was done because it was thought that cortisone administered at the time of burning might not be sufficiently absorbed to influence mor-

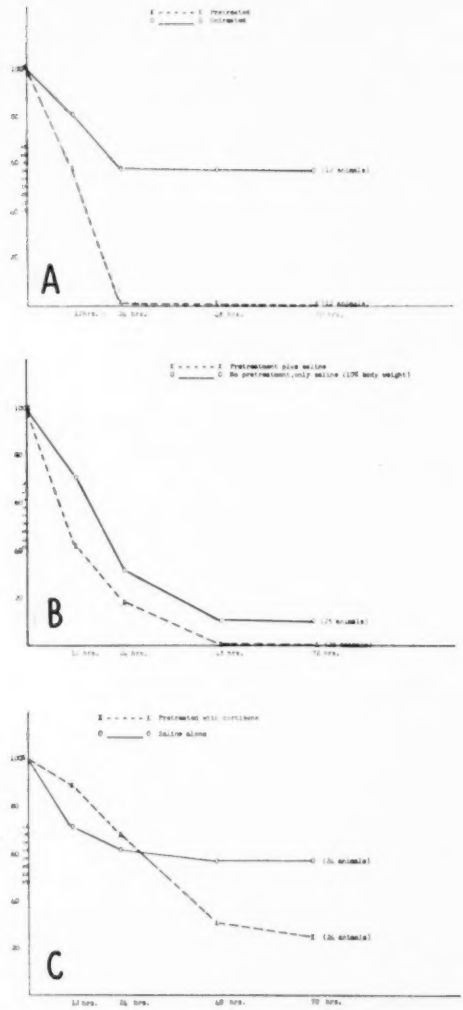

Chart 3.—*A*, effect of pretreatment with cortisone (5 mg. per day, four doses) on mortality of rats burned and not treated. *B*, effect of pretreatment with cortisone (5 mg. per day, four doses) on mortality of rats burned and treated with isotonic sodium chloride solution. *C*, effect of pretreatment with cortisone (2.5 mg. 12 hours before burn and 2.5 mg. at time of burn) on mortality of rats treated with isotonic sodium chloride solution (10% body weight).

tality. However, Chart 3*C* demonstrates, once again, an increased mortality following pretreatment with cortisone. Table 1 summarizes these experiments with cortisone.

The effect of treatment with corticotropin on the burn mortality in the rat was studied in Experiments 7, 8, and 9. Corresponding charts (Chart 4 *A*, *B*, and *C*) illustrate the survival curves, and Table 2 summarizes the data. It can be seen that, while pretreatment with corticotropin for seven doses prior to burning increased

TABLE 1.—*Summary of Data in Experiments with Cortisone*

Experiment		Treatment	No. of Animals	% 72-Hr. Survivals
1	a	0	50	14
	b	Isotonic sodium chloride solution, 10% body wt.	50	48
2	a	0	37	30
	b	Cortisone, 5 mg. daily	37	24
3	a	Isotonic sodium chloride solution, 10% body wt.	99	60
	b	Cortisone, 5-mg. single dose; isotonic sodium chloride solution, 10% body wt.	99	58
4	a	0	12	58
	b	Pretreatment for 4 days, 5 mg. cortisone daily	12	0
5	a	Isotonic sodium chloride solution, 10% body wt. at burn	25	10
	b	Pretreatment for 4 days, 5 mg. cortisone daily; isotonic sodium chloride solution at burn	25	0
6	a	Isotonic sodium chloride solution, 10% body wt.	24	55
	b	2.5 mg. cortisone 12 hr. prior to burning; 2.5 mg. cortisone and isotonic sodium chloride solution at burn	25	24

TABLE 2.—*Summary of Data in Experiments with Corticotropin*

Experiment		Treatment	No. of Animals	% 72-Hr. Survivals
7	a	0	75	14
	b	Corticotropin, 2.5 mg. every 12 hr. for 7 doses prior to burning	75	32
8	a	0	25	50
	b	Corticotropin, 2.5 mg. every 12 hr. for 7 doses prior to burning and every 12 hr. thereafter	25	24
9	a	Isotonic sodium chloride solution, 10% body wt.	25	16
	b	Isotonic sodium chloride solution, 10% body wt.; corticotropin, 2.5 mg. every 12 hr.	25	28

slightly the percentage of animals alive at 72 hours, the survival curves of the treated and untreated animals are almost identical, and we believe that the increase in the survival rate is probably not significant. Increased doubt that treatment with corticotropin is effective in increasing the survival rate of the burned rat is obtained from the inspection of Chart 4*B*. In Experiment 8 corticotropin was administered before burning and every 12 hours thereafter. Fewer treated animals survived than untreated animals. In Experiment 9 the group receiving isotonic sodium chloride solution plus corticotropin after burning did slightly better than the group receiving isotonic sodium chloride solution alone, although here, too, the survival curves are almost identical, and the difference is probably not significant.

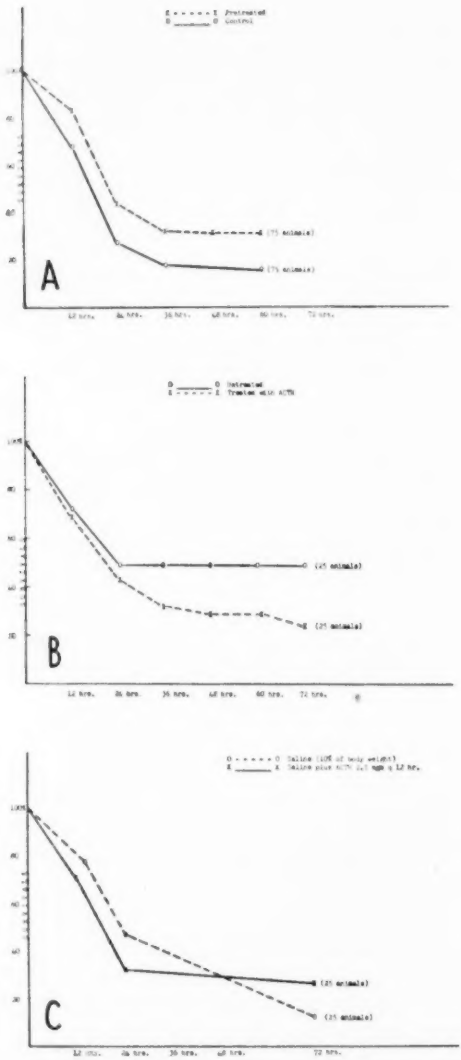

Chart 4.—*A*, effect of pretreatment with corticotropin (2.5 mg. every 12 hours for seven doses) on burn mortality. *B*, effect of pretreatment and post-treatment with corticotropin (2.5 mg. every 12 hours) on burn mortality. *C*, effect of treatment with corticotropin on mortality of rats burned and treated with isotonic sodium chloride solution.

Table 3 summarizes the data in experiments with desoxycorticosterone acetate. Experiment 10 consisted of the treatment of half a group of rats with 1 mg. of desoxycorticosterone acetate given each day for six days prior to burning. At the time of the final dose the animals were burned along with an equal number which received no treatment. No isotonic sodium chloride solution was given to either group. The mortality of the desoxycorticosterone-acetate-treated group was only one-half that of the untreated group. In Experiment 11 all animals were given isotonic sodium chloride solution at the time of burning, and every other animal was given, in addition, 1 mg. of desoxycorticosterone acetate at the time of burning and every 24 hours thereafter. The addition of desoxycorticosterone acetate may have slightly improved the survival rate. Experiment 12 demonstrates that the administration of desoxycorticosterone acetate fails to protect against the deleterious effect of treatment with cortisone. Similarly, Experiment 13 demonstrates

TABLE 3.—*Summary of Data in Experiments with Desoxycorticosterone Acetate*

Experiment		Treatment	No. of Animals	% 72-Hr. Survivals
10	a	0	50	20
	b	Desoxycorticosterone acetate, 1 mg. daily for 6 doses prior to burning	49	40
11	a	Isotonic sodium chloride solution at burn	50	22
	b	Isotonic sodium chloride solution at burn; desoxycorticosterone acetate, 1 mg. at burn and every 24 hr. thereafter	50	32
12	a	Isotonic sodium chloride solution at burn	25	32
	b	Isotonic sodium chloride solution at burn; cortisone, 5 mg.; desoxycorticosterone acetate, 1 mg. at burn and every 24 hr. thereafter	25	8
13	a	Cortisone, 5 mg.; desoxycorticosterone acetate, 1 mg. given every 24 hr. for 5 days prior to burning	25	12
	b	Cortisone, 5 mg. every 24 hr. for 5 days prior to burning	24	0

that the administration of desoxycorticosterone acetate fails to protect the animal against the harmful effect of cortisone given before burning.

COMMENT

Interpretation of these data is subject to several criticisms. In the first place, one wishes for a more standard burn. The variability of the burn mortality makes comparison of the various experimental groups difficult. Secondly, it might well be argued that the doses of desoxycorticosterone acetate, cortisone, and corticotropin employed were in each instance toxic doses. It is certain that with the dosages used toxic effects have been observed in animals which were subjected to no additional stress. Ingle has reported [5] that if rats are given cortisone, 5 mg. per day, the mortality at the end of 21 days is approximately 50% and that gastrointestinal ulceration, fatty livers, and gross renal and cardiac pathological lesions are observed. Similarly, the toxicity of corticotropin and desoxycorticosterone acetate in large doses is well known. However, in our experiments the effects of the agents were almost always those of a single dose. Inspection of the mortality curves indicates that the shape of the curve in the first 24 hours determines the subsequent 72-hour mortality figure. Hence, the increased mortality of the animals burned and treated with cortisone cannot entirely be due to the long-term chronic toxicity of cortisone.

CONCLUSIONS

From our data we draw the following conclusions:

1. The remarkable effect first described by Rosenthal of the administration of isotonic sodium chloride solution in amounts equal to 10% of body weight in reducing the mortality of burn shock is affirmed.

2. Cortisone treatment after burning does not increase the survival rate of rats with 30% of the body surface burned at 85 C. for 30 seconds.

3. Pretreatment with cortisone distinctly lowers the survival rate of the burned rat. This observation confirms the findings of Kay and Delaney.[14]

4. Corticotropin (ACTH; adrenocorticotropic hormone) given before or after burning does not significantly alter the survival rate of the burned rat.

5. We confirm the demonstration of You and Sellers that desoxycorticosterone (DOCA*) acetate given before burning protects the rat against burn shock.

6. Desoxycorticosterone acetate treatment does not markedly enhance the protective effect of isotonic sodium chloride solution given in amounts equal to 10% of body weight.

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SECONDARY CARCINOMA OF THE PENIS ARISING FROM CARCINOMA OF THE RECTUM

CHARLES NEY, M.D.
NEW YORK

SECONDARY carcinoma of the penis is exceedingly rare. Wattenberg,[1] in 1944, collected 19 cases from the literature and added 1 of his own. Since 1944, as far as I can ascertain, 13 additional cases [2] have been described. Of the total number (33) of cases which have been reported, in 7 the primary tumor was in the rectum. Niewiesch,[3] Matheson,[4] Stein and Hantsch,[5] Kerr and Gillies,[2a] Melicow and Ganem,[2b] Thompson,[2f] and Cattell and Mace [2i] have reported these cases.

Recently, a patient with secondary carcinoma of the penis arising from a carcinoma of the rectum came under my care whose case I believed worth while reporting because of its rarity.

REPORT OF A CASE

W. H., a 52-year-old white man, was admitted to Montefiore Hospital on Nov. 27, 1948, with the main complaint of pain in the right leg. His present illness began four years previously, when constipation and melena developed, and the condition was diagnosed as a malignant tumor of the rectum. He was operated upon at Presbyterian Hospital, November, 1944, and a

1. Wattenberg, C. A.: Unusual Tumors and Secondary Carcinomas of the Penis: Review of the Literature and Report of a Case, J. Urol. **52**:169-175 (Aug.) 1944.

2. (*a*) Kerr, H. D., and Gillies, C. L.: The Urinary Tract; a Handbook of Roentgen Diagnosis, Chicago, The Year Book Publishers, Inc., 1944, p. 298. (*b*) Melicow, M. M., and Ganem, E. J.: Cancerous and Precancerous Lesions of the Penis, J. Urol. **55**:486-514 (May) 1946. (*c*) Musiani, V.: Della rarità delle metastasi carcinomatose nei corpi cavernosi del pene, Urologia **14**:94-97 (April 20) 1947. (*d*) Burrell, N. L.: Priapism Due to Metastatic Hypernephroma in Corpora Cavernosa Penis, J. Urol. **60**:636-639 (Oct.) 1948. (*e*) Markson, L. S.; Stoops, C. W., and Kanster, J.: Metastatic Transitional Cell Carcinoma of the Penis Simulating a Chancre, Arch. Dermat. & Syph. **59**:50-54 (Jan.) 1949. (*f*) Thompson, H. T.: Involvement of the Penis by Carcinoma of the Rectum, Surgery **27**:216-220 (Feb.) 1950. (*g*) Henderson, D. St. C. L.: A Case of Persistent Priapism Secondary to a Transitional Cell Carcinoma of the Left Kidney, Brit. J. Urol. **22**:223-227 (Sept.) 1950. (*h*) Klinger, M. E.: Secondary Tumors of Genito-Urinary Tract, J. Urol. **65**:144-153 (Jan.) 1951. (*i*) Cattell, R. B., and Mace, A. J.: Metastasis to the Penis from Carcinoma of the Rectum, J. A. M. A. **146**:1230-1231 (July 28) 1951. (*j*) Fort, C. A.; Bailey, M. K., and Kicklighter, J. E.: Primary Carcinoma of Bladder with Secondary Metastasis to Penis, J. Urol. **66**:238-241 (Aug.) 1951.

3. Niewiesch, H.: Priapismus bei primären und metastatischen Geschwülsten in den Schwellkörpern der Penis, Deutsche Ztschr. Chir. **241**:94-103, 1933.

4. Matheson, N. M.: Secondary Carcinomatous Deposits in Body of Penis: Retention of Urine, Urol. & Cutan. Rev. **39**:566-567 (Aug.) 1935.

5. Stein, J. J., and Hantsch, F. K.: Adenocarcinoma of Rectum with Unusual Sites of Metastases, J. A. M. A. **108**:1776-1779 (May 22) 1937.

resection of the rectum with a permanent colostomy was performed, with use of spinal anesthesia. The report on the specimen removed at operation is reproduced here in part, with the permission of Dr. A. P. Stout.

"The specimen consists of the sigmoid colon, rectum, anal orifice, and surrounding perianal tissue. A firm mass can be felt and seen constricting the anal orifice.

"When the specimen is opened along the anterior wall, a fungating, ulcerating mass can be seen at the anal orifice along the posterior wall of the rectum. This mass measures 5 cm.

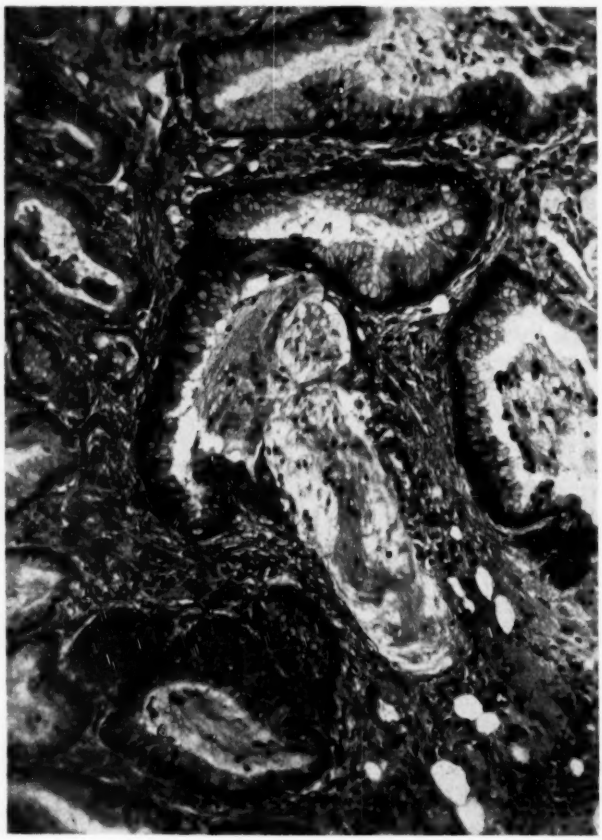

Fig. 1.—Section of the original tumor of rectum removed by abdominal-perineal resection: × 145.

in greatest diameter. The 24 cm. of rectum and sigmoid above the lesion shows no gross pathology."

Microscopic Description (Figs. 1 and 2).—A section was taken through the tumor and the skin about the anus. The tumor cells were high cuboidal to columnar and had lost their basal nuclear polarity. These cells were arranged in acinar structures, which contained a stringy mucoid material. The tumor extended to the mucosa of the anal canal but did not infiltrate under the skin. The surface of the tumor was ulcerated, and there was a dense inflammatory reaction in this area. There was invasion of the smooth muscle, but the striated muscle in this section was not involved.

One of the other sections included the nine lymph nodes found in the region of the tumor. Four of these showed the presence of tumor cells. In these the substance of the node was completely replaced by large pools of mucoid material lined by tumor cells.

Diagnosis.—A diagnosis of carcinoma (colloid type) of the rectum with metastases to regional lymph nodes was made.

Postoperative Course.—Almost immediately after operation (Dec. 1, 1944), pain and weakness developed in the right leg, and the patient had difficulty in urinating. This difficulty included great urgency, dribbling, and trouble with emptying the bladder. All these symptoms gradually became worse. In June, 1945, the patient was seized with severe pain in the left anterior chest. He was again admitted to Presbyterian Hospital, and a diagnosis of coronary thrombosis was made. He remained there five weeks.

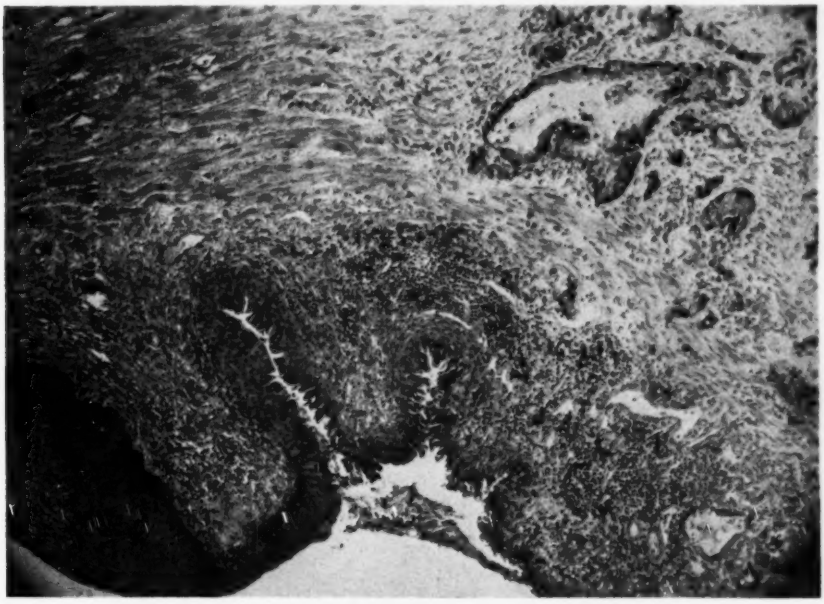

Fig. 2.—Photomicrograph showing extension of tumor to the region of mucosa of the anal canal; × 85.

In August, 1947, he was admitted to the urological service because of his bladder complaints. An intravenous pyelogram showed that both kidneys excreted the dye well and emptied normally. There was no gross dilatation of the upper urinary tract. The bladder shadow was slightly irregular and somewhat displaced to the left side of the pelvis. He was discharged 10 days after entering the hospital.

On Oct. 10 he was admitted to the Neurological Institute for relief of pain. In the six months prior to admission the pain in the right lower extremity had become progressively severer. X-ray studies revealed the lumbosacral portion of the spine and the pelvis to be normal. The differential diagnosis rested between metastatic carcinoma in the lymph nodes in the pelvis, with pressure upon the lumbosacral plexus, and arachnoidal adhesions within the spinal canal. It was believed that the former was the more likely; but, in any event, the problem was relief of pain, and therapy in either case was the same. Accordingly, a bilateral spinothalamic tractotomy was performed in the upper thoracic region at the second thoracic segment on the left and at the third thoracic segment on the right. When he was discharged from the hospital,

on Nov. 27, there was a sensory level for pain at the fifth thoracic dermatome on the right and at the sixth thoracic dermatome on the left.

He was readmitted to the urological service on Dec. 4, 1947, because of an elevation of temperature. A urinary-tract infection was found. The patient responded well to the administration of sulfadiazine and penicillin. He was discharged eight days after admission to the hospital. Shortly after he returned home, his temperature again rose but was rapidly controlled with streptomycin.

Fig. 3.—Biopsy specimen of penis. The anaplastic tumor contains distorted acini. Many of the cells are mucus-producing; × 145.

In the 11 months prior to his admission to Montefiore Hospital the patient became progressively weaker. He had intense pain in the right leg. For several months before entering the hospital, he had complete loss of motion in the right foot. Urination had become extremely difficult. He had to stand and strain to void, and voided only a small amount at a time. There was a constant desire to urinate. His bladder leaked occasionally, and the urinary stream became very thin. He could start and stop the stream voluntarily. One month before admission there developed a painful erection of the penis which was constant.

Physical Examination.—The patient, a moderately well-nourished man, complained bitterly of pain in the right leg and painful erection of the penis. There were no masses or tenderness in the head. The pupils were equal and regular and reacted to light and in accommodation.

The papillae and edges of the tongue were slightly atrophied. No abnormalities were noticed in the lungs on percussion or auscultation. Heart sounds were distant but of good quality; no murmurs were heard, and sinus rhythm was regular. There was a functioning colostomy stoma in the left lower quadrant, with weakness of the surrounding abdominal wall. No masses were palpable in the abdomen. The bladder was not up. A small inguinal hernia was present bilaterally. In the left axilla were several discrete, nontender, firm lymph nodes, 2 cm. in diameter. The rectum was absent. The testes were normal. There was persistent erection of the penis. On palpation, the corpora cavernosa were filled with firm, nonmovable, smooth nodules. These nodules varied from approximately 1 to 5 mm. in diameter. Practically the entire corpus cavernosum penis was involved bilaterally. The skin of the penis and the glans penis were free of nodules.

Neurological Examination.—There was loss of sensation to pinprick, heat, and cold from the seventh thoracic dermatome downward. Touch sensation, however, was intact. Both lower extremities were atrophied, the atrophy being slightly more marked on the right side. The right foot was paralyzed, with marked weakness of the right leg. There was some ability to flex at the right hip and knee. Knee and ankle reflexes were absent on the right but were 1+ on the left. The Babinski sign was not present.

Laboratory Findings.—The urine was acid, with a specific gravity of 1.020, and gave a 1+ reaction for albumin and a negative reaction for sugar. Microscopic study showed many white blood cells, no red blood cells, and no casts. Blood studies showed a hemoglobin concentration of 13 gm. per 100 cc., a red cell count of 4,140,000, and a white cell count of 9,900, with 67% polymorphonuclear leucocytes, 3% band forms, 20% lymphocytes, 8% metamyelocytes, and 1% eosinophiles. The Wassermann reaction was negative. The urea nitrogen measured 20.3 mg. and the blood sugar 90 mg. per 100 cc. Roentgenograms revealed widespread metastatic lesions in the lungs and osteoblastic lesions in the second lumbar vertebra, left ilium, sacrum, right ilium, right ischium, and right pubis. Changes in the right pubis and the right ischium were osteoclastic, as well as osteoblastic.

Course in the Hospital.—Voiding became increasingly difficult, and a catheter could hardly be passed because of irregular resistance all along the anterior urethra. On Dec. 21, 1948, a suprapubic cystostomy was performed, using a No. 28 Pezzar tube. No nodules were palpable in the region of the vesical neck. At the same time a biopsy of the penis was performed, which was reported by Dr. David Spiro as follows:

"The specimen consists of a tumor nodule, the stroma of which is loose, edematous, and vascular. The tumor is highly anaplastic and consists of small nests and irregular clumps of cells, as well as of distorted acini (Fig. 3). The cells vary in size and shape. Many are mucus-producing. Signet-ring forms are not infrequent. The nuclei are large, bizzare in shape, and mostly hyperchromatic; mitotic activity is present to a moderate degree."

Diagnosis.—A diagnosis of metastatic anaplastic adenocarcinoma was made.

Postoperative Course.—After cystostomy the patient felt somewhat more comfortable. Ten days after his operation he was discharged home, where he remained in bed. He continued to complain of pain in the right leg and the lower abdomen. The tube functioned fairly well. His appetite gradually lessened until one month after leaving the hospital, when he almost stopped eating altogether. He lost weight and became weaker. On March 14, 1949, he complained of blurring of vision and double vision. Paralysis of the left external rectus muscle was found. Several days later the right external rectus became paralyzed. The pupils were regular and widely dilated. The eyegrounds could not be distinctly visualized but seemed grossly normal. A bedsore was seen over the sacrum approximately two weeks before his death. He gradually deteriorated, and bronchopneumonia developed at the base of the right lung terminally. He died April 5, 1949. Permission for autopsy was not obtained.

COMMENT

The rarity of secondary carcinomatous deposits in the penis from carcinoma of the rectum is striking, considering the proximity of the organs. The most widely accepted view of the mode of invasion is that of direct extension.

Actually, the explanation of the spread of cancer from the rectum to the penis is difficult because of the difference of opinion concerning the anatomy of the region. This is readily recognized after studying the reports of Wesson,[6] Tobin and Benjamin,[7] and Uhlenhuth and associates.[8]

The consensus places the area of break-through in the region of the superficial perineal pouch, that is, between the urogenital diaphragm and its inferior covering, the perineal membrane, and the superficial perineal fascia (Colles).

It would appear that the anal canal proper is in relation to this area, and therefore the lower the growth is situated in the rectal canal, the greater the chance of spread by direct extension to the penis. Unfortunately, the reports in the literature do not clarify the exact position of the growth, except for those of Stein and Hantsch,[5] Thompson,[2f] and Cattell and Mace.[2i] The growth described by Stein and Hantsch was 6 cm. from the anal margin; that by Thompson, 3 cm. above the sphincter, and that by Cattell and Mace, 2 cm. proximal to the mucocutaneous line. In the present case the carcinoma was at the lowermost point of the rectum, as can be seen in Figure 2, where the squamous epithelium bordering the new growth is clearly visible. Since the lowermost portion of the rectum lying within 1 in. (2.5 cm.) of the anorectal line is less frequently involved with carcinoma than any other portion of the rectum,[9] the rarity of extension to the penis is partially explained. Of course, this is not the complete answer, since the last 1 in. of the rectum still accounts for 5.3% of new growths of the rectum and sigmoid.[10]

It is just as difficult to understand the infrequent involvement of the urethra in any case of secondary invasion of the penis. Wattenberg [1] stated that usually secondary carcinoma does not involve the urethra or the corpus spongiosum. Of the seven previously reported cases of carcinoma of the rectum with extension to the penis, in only two (Kerr and Gillies [2n] and Thompson [2f]) was definite involvement of the urethra mentioned. Matheson [4] described compression of the urethra, so much so, that retention of urine occurred. Catheterization showed marked narrowing of the lumen from about 1 in. behind the external meatus to the vicinity of the bulb. In the case reported in this paper, the anterior urethra was narrowed, and irregularities could be felt throughout. Unfortunately, no autopsy was obtained, and whether the urethra was actually invaded or whether it was compressed by external nodules could not be ascertained. Thompson [2f] believed that if the corpus spongiosum is involved, the extension would probably have to take place through the urogenital diaphragm.

6. Wesson, M. B.: The Clinical Importance of Buck's and Colles' Fasciae, Surg., Gynec. & Obst. **44**:208-213 (Feb.) 1927.

7. Tobin, C. E., and Benjamin, J. A.: Anatomical Study and Clinical Consideration of the Fasciae Limiting Urinary Extravasation from Penile Urethra, Surg., Gynec. & Obst. **79**:195-204 (Aug.) 1944; Anatomical and Clinical Re-evaluation of Camper's, Scarpa's and Colles' Fasciae, ibid. **88**:545-559 (May) 1949.

8. Uhlenhuth, E.; Smith, R. D.; Day, E. C., and Middleton, E. B.: A Re-investigation of Colles' and Buck's Fasciae in the Male, J. Urol. **62**:542-563 (Oct.) 1949.

9. Bacon, H. E.: Anus-Rectum-Sigmoid Colon: Diagnosis and Treatment, Ed. 3, London, J. B. Lippincott Co., 1949, Vol. 1, p. 3.

10. Bacon, H. E.: Anus-Rectum-Sigmoid Colon: Diagnosis and Treatment, Ed. 3, London, J. B. Lippincott Co., 1949, Vol. 2, p. 602.

Priapism has been reported frequently in cases of secondary carcinoma of the penis. Of the seven cases of rectal carcinoma with metastases to the penis, priapism is mentioned in three. In the present case the priapism was persistent day and night (even during sleep) and was painful. In this particular case examination was not made after death, but in another case of secondary carcinoma of the penis in the files of the laboratory division of Montefiore Hospital it was reported that the penis remained large and rigid post mortem.

The cause of the priapism in these cases is not entirely explained. There is probably a combination of factors: (1) replacement of corpus cavernosum by tumor tissue; (2) stasis and thrombosis of sinuses in the corpora cavernosa not directly involved by the tumor process, and (3) ascending peripheral-nerve stimulation by tumor tissue, causing a reflex priapism.

SUMMARY

A case of carcinoma of the rectum with extension to the penis is described. This is the eighth reported case.

A review of the literature is presented.

The route of invasion and the cause of the priapism are discussed.

745 5th Ave. (22).

PRIMARY CARCINOMA OF THE BARTHOLIN GLAND TREATED BY RADICAL SURGERY

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JOHN BAUER, M.D.
AND
EUGENE M. BRICKER, M.D.
ST. LOUIS

PRIMARY cancer of the Bartholin gland is a rare disease. Crossen [1] reports an approximate incidence of 1 case of primary Bartholin gland cancer to every 1,000 cases of cancer of the female genital tract. A recent review of the literature by Wharton and Everett [2] shows that 109 verified cases have been reported. We are reporting another case of primary cancer of the Bartholin gland, not only because of the rarity of the lesion but because of its size and the unusual method of treatment in this case. The therapy consisted of pelvic evisceration and radical right groin dissection with removal of the right inguinal lymph nodes and vulva en bloc with the pelvic viscera. This surgical approach was used because the lesion was extensive and encroached upon both the urethra and the rectum. Adequate extirpation of the involved areas could not be accomplished by a less radical procedure.

REPORT OF A CASE

Patient F. W., a 54-year-old woman, nullipara, gravida 0, was admitted to St. Louis City Hospital on March 6, 1951, with the complaint of a lump in the right vulva of 17 months' duration, becoming progressively larger. At the onset the patient noticed a nodule in her right labium which was described as being rather deep in the tissue and fairly movable. Although this mass continued to grow larger, the patient was not concerned about its presence, for it was asymptomatic. She first became apprehensive one week before admission when a bleeding sore appeared in the vagina immediately above the growth. There were no genitourinary complaints other than slight burning on urination and nocturia. The history of symptoms was otherwise noncontributory. Past history revealed that the patient had been in the St. Louis State Hospital for the preceding 13 years 5 months with a diagnosis of "feeble-mindedness with psychotic episodes." The history was considered reliable despite her psychiatric diagnosis. She had always been in good general health until her present illness. In 1949 she had a supracervical hysterectomy because of a fibroid uterus.

Physical examination on admission showed her blood pressure to be 205/105, temperature 98.6 F., pulse rate 80, and respiration 16. Her physical examination, other than pelvic, revealed no abnormalities except for an enlarged heart and palpable right inguinal nodes, the largest being about 2 cm. in diameter. Pelvic examination showed the area of the right Bartholin gland to be replaced by an irregular firm mass measuring 4 by 5 by 5 cm. which was slightly tender and only partially fixed. This mass extended to the urethra above and to the rectum below. The skin and vaginal mucosa were intact except for one small ulcerated area in the vagina, about 0.5 cm. in diameter, immediately over the growth. The external genitalia and introitus

From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, and the Unit I Surgical Service, St. Louis City Hospital.

1. Crossen, R. J.: Primary Carcinoma of Bartholin's Gland, Am. J. Surg. **75**:597-600, 1948.

2. Wharton, L. R., Jr., and Everett, H. S.: Primary Malignant Bartholin Gland Tumors, Obst. & Gynec. Surv. **6**:1-8, 1951.

were normal. The cervix was small, clean, soft, and nulliparous. The uterus and adnexa were absent. On rectal examination a tumor mass deep in the right labium was revealed. This mass extended to, but not through, the wall of the rectum.

Preoperative examinations included an electrocardiogram, which suggested left axis deviation. Chest x-ray studies, proctoscopic examination, intravenous pyelography, barium enema visualization, palpation of the liver, and x-ray series for metastases showed no abnormalities. Biopsies of both the primary lesion and a right inguinal lymph node showed undifferentiated carcinoma. Surgical consultants were of the opinion that to extirpate the lesion adequately it would be necessary to sacrifice the urethra, bladder, and rectum.

On April 2, 1951, the patient had an operation which consisted of the following: excision en bloc dissection of the rectum, cervix and vagina, bladder and urethra, including the internal iliac veins and hypogastric arteries, and distal portion of both ureters. Both ureters were transplanted into an isolated segment of ileum, the distal end of which formed an ileostomy for urinary drainage. A left-sided colostomy was made for fecal drainage. The operative procedure was done as recently described by Bricker.[3] In addition, a complete right inguinal dissection and resection of the vulva en bloc with the pelvic viscera was accomplished. The

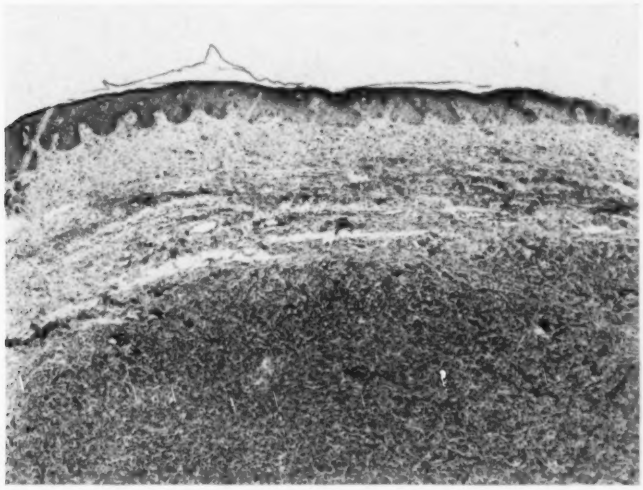

Fig. 1.—Photomicrograph showing tumor situated deep in dermis which is covered by regular stratified squamous epithelium; × 38.

postoperative course was relatively uncomplicated. The blood-urea-nitrogen level rose as high as 66 mg. per 100 cc. on the second postoperative day but decreased immediately thereafter. The patient was discharged to the St. Louis State Hospital on April 27, with a Rutzen bag applied to the ileostomy.

This patient was last seen in May, 1952, and at that time she had no complaints. There was no evidence of recurrence of the cancer. The urinary and fecal stomata were functioning satisfactorily.

Pathological Report.—Gross Description: The specimen consisted of the inguinal and iliac lymph nodes, as well as the vulva, vagina, cervix uteri (the corpus uteri is absent), ovaries, fallopian tubes, bladder with distal ends of both ureters, rectum, anus, and the surrounding pelvic fibroadipose tissue containing the respective groups of lymph nodes. The specimen was in one piece and had a total weight of 1,320 gm. In the posterior portion of the right labium minus, between it and the labium majus, was a hard tumor which measured 4 by 3.5 by 3 cm.

3. Bricker, E. M., and Modlin, J.: The Role of Pelvic Evisceration in Surgery, Surgery **30**:76-94, 1951; Bladder Substitution After Pelvic Evisceration, S. Clin. North America **30**:1511-1521, 1950.

The tumor extended along the posterior portion of the vestibulum vaginae. The surface was slightly depressed and irregular. There were two recent surgical incisions. The tumor had an adequate margin of excision and did not appear to extend into the cervix, bladder, or rectum.

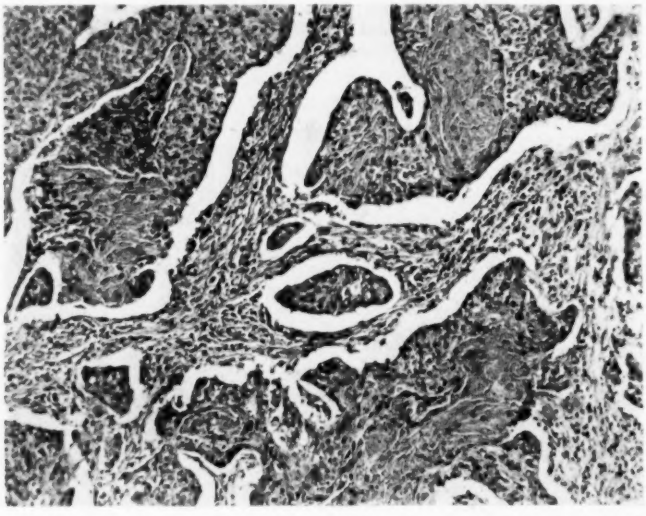

Fig. 2.—Photomicrograph showing representative area of tumor consisting of sheets of anaplastic squamous cells which form masses of keratin; × 90.

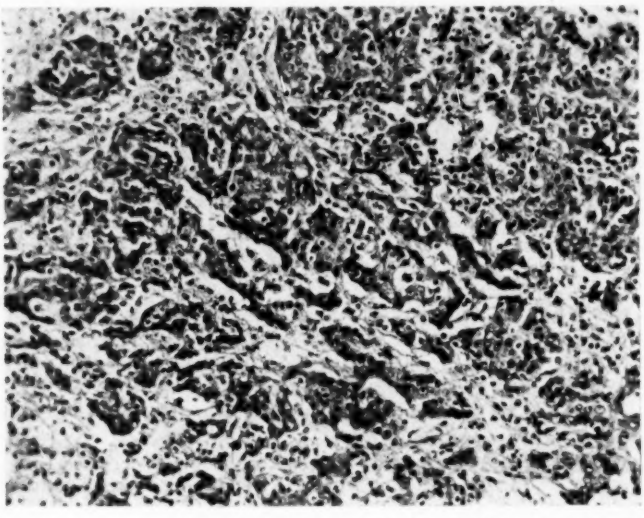

Fig. 3.—Photomicrograph of tumor showing anaplastic epithelial cells arranged in intertwining adenoid pattern. These cells surround collections of foamy macrophages; × 160.

Microscopic Description: Numerous sections of the labial lesion showed a fairly well circumscribed tumor, the bulk of which was situated in the dermis (Fig. 1), filling the space between the epidermis and the muscle layer. It invaded the epithelium inferiorly, causing a small area of ulceration. Superiorly the muscle was invaded. The tumor showed two growth

patterns. In some areas there were sheets of anaplastic epithelial cells resembling squamous cells which form keratin masses (Fig. 2). In other areas, thin cords of these cells formed an adenoid pattern (Fig. 3). Within the meshes of these cell groups were collections of foam cells and scattered giant cells. Large areas of the tumor were infiltrated with lymphocytes and large mononuclears. Step sections failed to show remnants of Bartholin gland tissue.

Lymph Nodes: Right iliac lymph nodes: Two nodes show invasion by keratinizing squamous carcinoma.

Right inguinal lymph nodes: Six nodes fail to show any invasion by tumor. Previous biopsy of nodes in this area revealed squamous carcinoma in one node.

Anterior inferior rectal lymph nodes: One shows invasion by the above tumor.

Pararectal lymph nodes: All are free of tumor.

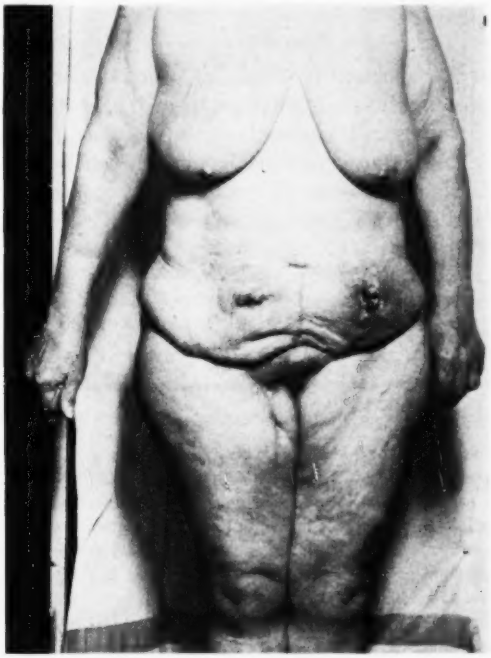

Fig. 4.—Photograph of Patient F. W. Patient is well and without evidence of recurrence.

Other Structures: Sections of cervix, bladder, ovaries, and rectum failed to show any tumor extension.

Diagnosis.—Block dissection of the pelvic viscera, the vulva, and the right inguinal region was carried out.

Lesion in the Area of the Bartholin Gland: The tumor was diagnosed as carcinoma with keratinizing squamous and adenoid elements. There was metastasis of the keratinizing squamous type to the regional lymph nodes.

COMMENT

We feel that both clinically and pathologically this case presents a primary carcinoma of the Bartholin gland, and we therefore add it to those already reported in the literature. In arriving at a diagnosis of Bartholin gland carcinoma, we have been guided by the criteria laid down by Honan [4] and Schaeffer.[5] Clinically, the history, location, and course of the disease follow the recognized pattern of primary

carcinoma of the Bartholin gland. Pathologically in favor of this diagnosis are the following findings: 1. The superficial epithelium fails to show Bowenoid changes, as frequently seen in primary tumors of skin origin. 2. The bulk of the tumor is situated deep in the dermis, covered for the most part by intact epithelium. 3. Large areas of tumor show an adenoid pattern similar to that seen in skin appendage tumors. 4. The foam cells might be due to some preexisting secretion.

The surgical attack used in the treatment of the lesion was unusual. It was necessitated by the proximity of the tumor to the rectum and urethra. It is of interest that there were metastases to the iliac lymph nodes and to the pararectal lymph nodes which could have been removed only by such a radical surgical approach.

SUMMARY

A case of primary carcinoma of the Bartholin gland is reported. This lesion was large and had metastasized to the right inguinal and right iliac lymph nodes and to the pararectal lymph nodes. It was treated by en bloc iliac lymph node dissection, pelvic evisceration, vulvectomy, and right inguinal lymph node dissection. The patient is well and without evidence of recurrence 13 months following removal of the tumor (Fig. 4). This patient was still without evidence of recurrence on Oct. 23, 1952.

4. Honan, J. H.: Über die Carcinome der Glandulae Bartholini, Berlin, E. Ebering, 1897.
5. Schaeffer, R.: Carcinom der Glandula Bartholini: Demonstration, Ztschr. Geburtsh. u. Gynäk. **50**:193, 1903.

CORRECTION

In the article by Drs. Martin and Morton on "Clinical Studies with the Electrogastrograph" printed in the September issue, page 382, the following changes should be made: Dr. Morton's initials are H. S. On page 384 the sixth sentence of the second paragraph should read: "The electrodes are reproducible to within 1 or 2 mv., but once made they must be treated with care, since they are photosensitive." In the second paragraph on page 392 the position of the last two sentences should be reversed. Footnote 35 should read "Gray, M.; Hokin, L. E., and Rehm, W. S.: *Am. J. Physiol.* **155**:440, 1948."

In the article by Drs. dePeyster, Paul, and Gilchrist on "Risk of Urgent Surgery in Presence of Myocardial Infarction and Angina Pectoris," page 448 of the September issue, the following changes should be made: The two items under I. Anterior Myocardial Infarction (*a*) in the outline on page 449 should read: "1. Q wave 0.04 second or more in duration in any lead from VI through V_6 in absence of right ventricular hypertrophy or right bundle branch block. 2. Q-S complex in any precordial lead to the left of the transition zone." The second item under I. Anterior Myocardial Infarction (*b*) should read: "2. History of chest pain with serial changes in the left precordial leads without significant Q waves but with change of one or more T waves from upright to inversion of at least 2 mm. lasting over 48 hours associated with fever and/or elevated sedimentation rate and/or an elevated white blood count." On page 453 the last line of Case 1 should read: "A rise in blood pressure and a return of normal color was achieved by the administration of oxygen, but later evidence showed the presence of an undoubted new myocardial infarction."

ACUTE FREE PERFORATION OF PEPTIC ULCER: COMPLICATION OF ULCER DIATHESIS

One Hundred Thirty-Nine Consecutive Cases

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AND
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THE PLICATION of an acute free perforation of a peptic ulcer is one of the simpler surgical procedures that for a long time has been regarded as a life-saving operation. The morbidity and the mortality rates associated with most surgical procedures have decreased decade by decade since they were first employed commonly. A review of the recent clinical reports from 1946 to 1952[1] (Table 1) reveals that there has been little improvement with this procedure over the past 30 years. In studying our 19-year experience at the New York Hospital-Cornell Medical Center, we have become interested in finding reasons for this seeming lack of progress, with the hope that measures might be devised to improve our results.

CLINICAL MATERIAL

One hundred thirty-six pavilion patients had 139 perforations treated by plication in 19 years. We have not included subacute perforations (penetrating ulcers), perforations into adjacent structures, or carcinomas with perforations in this series. The group was arbitrarily divided into two periods, 1932 to 1943 and 1944 to 1950,

From the department of Surgery, New York Hospital-Cornell Medical Center.

1. Moore, S. W., and Hendricks, R.: Late Results Following Perforated Peptic Ulcer, Surgery **23**:442-449, 1948.

2. (*a*) Brown, R. B., and Andrus, D. L.: Penicillin in the Postoperative Treatment of Peptic Ulcer with Perforation and Appendicitis with Operation, Ann. Surg. **138**:57-65, 1948. (*b*) McElhinney, W. T., and Holzer, C. E., Jr.: Factors Influencing Mortality from Acute Perforated Peptic Ulcers, Surg., Gynec. & Obst. **87**:85-92, 1948. (*c*) Eckhout, G. V.: Critique of Mushroom Catheter Treatment of Acute Gastroduodenal Perforation, A. M. A. Arch. Surg. **64**:111-118, 1952. (*d*) Tullis, R. H.: Perforated Gastroduodenal Ulcer, Am. J. Surg. **78**:490-495, 1949. (*e*) Baritell, A. LaM.: Perforated Gastroduodenal Ulcer, Surgery **21**:24-33, 1947. (*f*) Thompson, H. L., and Prout, H.: Surgical Treatment of Peptic Ulcer, Arch. Surg. **54**:390, 1947. (*g*) Estes, W. L., and Bennett, E. A., Jr.: Acute Perforation in Gastroduodenal Ulceration, with Special Reference to End-Results, Ann. Surg. **110**:321, 1944. (*h*) Luer, C. A.: Acute Perforations of Stomach and Small Bowel Ulcerations, Surgery **25**:404, 1949; Follow-up Report of One Hundred and Two Cases of Perforated Peptic Ulcers, ibid. **27**:360-363, 1950. (*i*) Johansson, O.: 200 Fälle von perforierenden Magen und Duodenalgeschwuren, Acta chir. scandinav. **95**:233, 1947. (*j*) Sangster, A. H.: Perforated Peptic Ulcer, Lancet **2**:289, 1948. (*k*) Kingsbury, H., and Peacock, E.: Acute Perforation of Peptic Ulcer, Surg., Gynec. & Obst. **92**:717, 1951. (*l*) Turner, F. P.: Acute Perforation of Stomach, Duodenum and Jejunum, ibid. **92**:281, 1951.

since during the latter time the patients were treated with antibiotics. The full series, however, is presented as a unit, unless there were significant differences in the two groups.

NUMBER OF PATIENTS AND SEX

The 136 patients in our series had 139 acute perforations which were due to peptic ulcerations. In three patients perforations occurred twice, but each perfora-

TABLE 1.—*Acute Free Perforation of Peptic Ulcer (Review of Clinical Reports 1946 to 1952)*

Author	Locality	No. of Patients	% Men	% Previous Ulcer History	% X-Ray Evidence Air Under Diaphragm	Location of Ulcer, % Duodenal or Pyloric	% Mortality
Moore and Hendricks [1]	Bellevue Hospital, New York	101	96.0	76.0	....	16.8	18.0
Brown and Andrus [2a]	Philadelphia	42	100.0	57.0	63.0	66.6	4.8
McElhinney and Holzer [2b]	Cincinnati	336	96.2	87.0	66.0	84.7	21.7 (1935-1937) 10.7 (1944-1946)
Eckhout [2c]	Denver	156	84.0	....	....	62.0	8.9
Tullis [2d]	Rochester, N. Y.	108	93.5	66.0	48.6	64.7	19.4 (2.9 last 10 yr)
Baritell [2e]	Oakland, Richmond, Calif.	88	97.1	64.8	58.5	89.8	7.1
Thompson and Prout [2f]	Los Angeles	100	87.0	32.0	66.0	53.0	15.0
Estes and Bennett [2g]	Bethlehem, Pa.	80	97.5	96.3	72.3	78.7	8.7
Luer [2h]	Fort Riley, Kan.	302	95.3	85.0	72.1	72.1	18.2
Johansson [21]	Gefle, Sweden	200	88.0	87.0	77.0	56.5	16.5
Sangster [2j]	Scotland	105	....	76.0	....	82.8	3.9
Kingsbury and Peacock [2k]	Roosevelt Hospital, New York	170	90.0	85.0	70.0	88.2	10.0
Turner [2l]	Presbyterian Hospital, New York	185	85.0	91.9	....	73.7	13.5 (8.3 last 4 yr)
Glenn and Harrison	New York Hospital, New York	139	92.0	87.7	57.4	82.0	11.5
	Total patients	2,172					

TABLE 2.—*Distribution by Age*

Age Group, Yr.	No. of Patients
15-19	1
20-29	14
30-39	35
40-49	43
50-59	34
60-69	12
	139

tion was tabulated separately, since it was considered an individual surgical emergency, the patient being subjected to the hazards of the disease each time. Of the 139 patients 128 (92%) were men.

AGE

The average age of the patients was 44.3 years. Table 2 shows that the group aged 40 to 49 years is the largest, with fairly even distribution in both the younger and older groups. The youngest person was aged 19 years, the oldest, 68 years.

PAST HISTORY

As a rule, acute perforations do not occur suddenly and dramatically without any forewarning symptoms of ulcer. Of our patients 122 (87.7%) had pain which was ulcer-like in character for over a week prior to the acute episode of perforation. Twelve (8.6%) denied having any pain or indigestion before the present illness. Table 3 shows the duration of the disease prior to perforation. Ninety-nine patients (71.1%) in the group had symptoms for over a year.

DURATION OF ACUTE SYMPTOMS AND PROGNOSIS

It is often stated that the duration of symptoms prior to hospitalization and surgical treatment has a direct bearing on the prognosis of perforation. In many instances we have found it difficult to determine whether the ulcer was penetrating

TABLE 3.—*Duration of Pain Prior to Perforation*

Less than 1 mo.	11
1 to 11 mo.	12
1 to 5 yr.	44
5 yr. or longer	55
	122

TABLE 4.—*Estimated Time Lapse Between Perforation and Hospitalization with Mortality Rate*

Time Lapse, Hr.	No.	Deaths	Mortality, %
0 to 3	65	4	6.1
4 to 8	39	6	15.1
9 to 12	13	2	15.1
Over 12	22	4	18.1
	139	16	11.5

or if it had definitely perforated. In this series there were 65 cases (46.8%) in which the history was compatible with perforation of less than three hours' duration. Four of these patients died, a mortality of 6.1%. There were 22 cases of perforation (15.8%) in which there was severe pain for over 12 hours, and four of these patients died, a mortality of 18.1%. Table 4 gives the estimated time interval between perforation and hospitalization and the subsequent mortality rate.

CONDITION ON ADMISSION

With few exceptions, all patients representing the 139 perforations were acutely ill on admission, but only 7 were considered moribund or in shock. Because of the small number of cases in this series, little can be derived from the mortality rate, but it might justifiably be expected to be high.

X-RAY EVIDENCE OF AIR UNDER THE DIAPHRAGM

Of the 80 patients with perforations in the 1932 to 1943 period, 38 had x-rays taken of the abdomen and diaphragm. The x-rays of 17 of these (44.7%) showed positive evidence of air under the diaphragm. In the ensuing 6-year period, 1944

to 1950, 56 of the 59 patients with acute perforations had x-rays taken. In 37 of these x-rays (66.1%) the findings were positive. This is in keeping with recent figures from other clinics.

PREVIOUS GASTROINTESTINAL SURGERY

Eight patients in the series had had previous perforated ulcers plicated, while two others had had gastroenterostomies. One of the latter two had a perforated duodenal ulcer, the other a perforated marginal ulcer. One patient had had two previous subtotal gastric resections yet was readmitted with a perforated marginal ulcer. This is an example of how severe the ulcer diathesis can be, as manifested by the perforation. Of the three patients in this series in whom perforations had occurred twice, two had duodenal perforations and the third a pyloric perforation.

ANESTHESIA

The anesthetic agent of choice was either cyclopropane or ether, with thiopental (pentothal*) sodium or nitrous oxide used for induction. Eight patients, however, were given local anesthesia and eight others spinal anesthesia. More important to us, however, than the type of anesthesia is its administration. With the decided improvement over the years in the administration of anesthesia the morbidity from complications resulting from anesthesia has decreased markedly.

TYPE OF OPERATION

Simple plication was done for all but three patients. Only drainage was done for these three because of the dense adhesions present which had already sealed off the perforation, and because it was felt that the general condition of the patients would not sustain a more arduous procedure. Gastroenterostomy was done in addition to plication in one case and gastroenterostomy with pyloric exclusion in another. Gastric resection was not carried out for any patient in this series.

LOCATION OF ULCER

At the time of operation, the surgeons occasionally had difficulty in determining whether the perforation had occurred in the duodenum or in the pylorus, since the pyloric landmarks were so obscured by edema and tissue reaction. Their opinions were recorded, however. Of the perforations 23 (16.6%) were considered to be gastric; 22 (15.8%) pyloric; 92 (66.2%) duodenal, and 2 (1.4%) marginal.

MORTALITY

Since there has been no basic change in the surgical approach to the problem of perforation over the past 15 years, any improvement in recent results must be attributed to better preoperative and postoperative care, to better anesthesia, and to the use of antibiotics. The operative mortality for the entire series was 16 deaths (11.5%). A comparison of the two periods is disappointing. There were 10 deaths in the group of 82 patients during 1932 to 1943, a mortality of 12.2%; in the 1944 to 1950 group of 59 patients there were 6 deaths, an only slightly better rate of 10.2%. The 16 deaths have been tabulated in Table 5 in an effort to show the clinical course and established or presumed cause of death. Ten of the 16 patients are believed to have died of generalized peritonitis with overwhelming infection.

TABLE 5.—*Analysis of Sixteen Deaths Following Acute Free Ulcer Perforation (the New York Hospital 1932 to 1950)*

Case No.	Year	Age, Yr.	Sex	Previous Ulcer Pain	Time Interval, Hr.	Anesthesia	Location of Perforation	Antibiotics	Postoperative Day of Death	Autopsy	Cause of Death
2-768	1932	32	M	3 yr.	12	Local	Pyloric	None	1st	Yes	Generalized peritonitis
20-016	1933	47	M	4 yr.	8	Local	Duodenal	None	8th	Yes	Generalized peritonitis; paralytic ileus
44-341	1933	33	M	None	26	Ethylene ether	Duodenal	None	2nd	No	Pulmonary embolus (delirium tremens)
94-150	1935	28	M	2 mo.	2½	Local ether	Duodenal	None	9th	No	Entered with acute glomerulonephritis; perforated while under treatment; died in uremia
127-880	1936	58	M	30 yr. (atypical)	1	Ethylene	Duodenal	Antipneumococcus serum	21st	No	Postoperative bronchopneumonia
206-133	1938	62	M	6 mo.	3 wk.	Local	Gastric *	None	18th	Yes	Multiple gastric ulcers; generalized peritonitis
160-960	1939	35	M	5 mo.	5	Ether	Duodenal	None	26th	Yes	Generalized peritonitis; nodular cirrhosis
116-262	1940	51	M	5 yr.	6	Spinal	Duodenal	None	34th	Yes	Bronchopneumonia following gastric resection for bleeding 28 days after plication; died 6th postoperative day
371-776	1943	46	M	5 yr.	2	Ether	Duodenal	Sulfadiazine	39th	No	Subdiaphragmatic, subphrenic, and left temporal abscesses
343-860	1943	43	M	None	5	Ether	Pyloric	Sulfadiazine	7th	Yes	Subdiaphragmatic, multiple liver, and pulmonary abscesses; multiple pylephlebitis
399-108	1944	41	M	None	24	Cyclopropane	Duodenal	Sulfadiazine	3rd	Yes	Delirium tremens; generalized peritonitis; multiple duodenal ulcers with perforation
350-538	1944	46	M	3 yr.	1	Ether	Duodenal	Sulfadiazine	21st	Yes	Postoperative hemorrhage; generalized peritonitis; multiple ulcers
306-529	1945	59	M	17 yr.	8	Spinal	Pyloric	Penicillin	1st	Yes	Arteriosclerotic heart disease with stenosis of anterior descending coronary artery; old anterior apical infarct
486-380	1947	68	M	None	1 wk.	Local Cyclopropane	Gastric	Penicillin, streptomycin, sulfadiazine	1st	Yes	Generalized peritonitis; edema and hyperemia of lungs
438-165	1949	55	M	25 yr.	8	Cyclopropane	Duodenal	Sulfadiazine, streptomycin, penicillin	9th	Yes	Perforated bleeding gastroesophageal ulcer, with generalized peritonitis and subdiaphragmatic abscess
581-779	1950	65	M	12 yr.	4	Ether	Duodenal	Penicillin, streptomycin, sulfadiazine	5th	No	Cerebral thrombosis

* With exploratory laparotomy there was no closure.

That this cause of death must still be reckoned with is brought out by the fatalities occurring as late as 1950, when such drugs as penicillin, streptomycin, and the sulfonamides had been in use for some time. One patient died after a secondary operation because of primary postoperative gastrointestinal hemorrhage. Two patients died of pulmonary complications, but they died in 1936 and 1940, respectively. Since the introduction of chemotherapy no deaths have been attributed to this cause. The patient who underwent a secondary gastric resection because of postoperative gastrointestinal bleeding subsequently died of pneumonia. The four remaining deaths were attributed to a variety of causes. One patient died of cerebral thrombosis; one of coronary occlusion; one, admitted originally with acute glomerulonephritis, died in uremia, and the fourth died of a possible pulmonary embolus.

TABLE 6.—*Complications Following Ulcer Perforation (the New York Hospital 1932 to 1950)*

1. Wound	
Infection	11
Dehiscence	2
	13
2. Ulcer activity	
Obstruction	
Complete	3
Incomplete	1
Bleeding	1
	5
3. Pulmonary	
Bronchopneumonia	16
Atelectasis	5
Lobar pneumonia	2
	23
4. Vascular	
Femoral artery thrombosis	1
Phlebothrombosis with pulmonary infaret	1
	2
5. Miscellaneous	
Subphrenic abscess	2
Alkalosis	1
	3
Total no. complications	46

but no autopsy was performed. At autopsy 4 of the 11 patients were found to have multiple mucosal ulcerations, but only one patient was found to have had two ulcers perforating simultaneously. One of these ulcers was found high on the lesser curvature at the esophageal-gastric junction and was not recognized at the time of operation.

It might be expected that the use of antibiotics would reduce the number of complications. Unfortunately, we have found only a slight decrease since their introduction. Twenty-five patients had 32 complications in the earlier series (1932 to 1943), a morbidity of 35.7%, while in 13 patients 14 complications developed in the later group (1944 to 1950), a morbidity of 24.5%. The only significant difference was seen in pulmonary complications, which comprised 56.3% of the complications in the earlier group and 35.7% in the later series. This drop accounted for the over-all reduction in morbidity and can be attributed to earlier ambulation as well as to the use of antibiotics. The complications are enumerated in Table 6.

POSTOPERATIVE FOLLOW-UP

We were able to follow 119 of the 123 patients who survived surgery for their perforation. This is a 96.8% follow-up. Since the results in both groups were found to be rather similar in spite of only a short-term follow-up for the later series, the early and late periods are not separated.

Four of the 119 patients followed up died subsequently: one died of bleeding ulcers at another hospital, one of carcinoma of the pancreas about three months later, and two elsewhere of unknown causes. The four deaths are not included in the follow-up results. Of the remaining 115 patients, only 35 (30.5%) remained asymptomatic. Eighty patients (69.5%) had recurrence or persistence of their ulcer symptoms. Twenty-five (21.7%) were controlled by strict medical measures. Fifty-five (47.8%) continued to have persistent pain, obstruction, or bleeding. Three of these patients were readmitted for reperforation. Forty-seven (40.9%) were subjected to secondary definitive surgery, which included 40 gastric resections, 4 gastroenterostomies, 2 vagotomies combined with gastroenterostomy, and 1 vagotomy. Five patients continued to have pain which remained unrelieved by conservative measures, but they refused further surgery.

COMMENT

The statistics of age and sex for this series are in line with those of other clinics. Of particular clinical interest is the fact that the majority of these patients (87.7%) had ulcer symptoms prior to their acute episodes of perforation. This again stresses the importance of an accurate history of a patient with an acute condition of the abdomen, which may be the clue needed to establish a correct diagnosis. Of similar interest is the added fact that over half the patients with history of ulcer symptoms had had their symptoms for more than five years. This may have contributed to the course of their disease after perforation. Various theories have been advanced as to what precipitates perforation. The time of day, the season of the year, or the relationship to heavy food intake were not found to be significant factors. It is well known, however, that in many patients perforation occurs during times of emotional stress, which substantiates the theory that a perforation is the result of severe ulcer diathesis.

Some observers contend that the serious nature of an ulcer diathesis, particularly in those who sustain a perforation, requires more definitive surgery than mere plication of the perforation.[3] We do not subscribe to this policy. Though the majority of the patients were in fair or good condition before operation, they were still all seriously ill, and many would not have been able to withstand a longer procedure. Furthermore, technical difficulties are increased in the presence of perforation because of the acute process and its associated inflammation. These conditions, we believe, would contribute to a much higher mortality if more than simple closure of the perforation were done. It is our practice to plicate the perforation transversely, and after closure to fasten a small tab of omentum to the area. We do not drain the area routinely.

Within the past six years, we have found air present under the diaphragm in 66.1% of the patients x-rayed. Recently, we have placed greater emphasis on this

3. Auchincloss, H., Jr.: Immediate Subtotal Gastrectomy for Acute Perforated Peptic Ulcer, Ann. Surg. **135**:134-138, 1952.

examination as a means of diagnosis. The patient should be placed in a sitting or semierect position for a few minutes to facilitate the collection of air. In addition, two lateral films to demonstrate air beneath the posterior diaphragmatic leaf are helpful. While x-rays that demonstrate free air support a diagnosis of perforation, it must be remembered that nonvisualization of free intraperitoneal air does not rule out a diagnosis of perforation.

It is important to evacuate the gastric contents preoperatively, because such evacuation lessens the possibility of regurgitation during induction of anesthesia, and it diminishes the amount of material that may soil the peritoneal cavity. Postoperatively, one hazard is the development of a subphrenic or pelvic abscess. It is rather easy to remove the free gastric material in the subhepatic area, but the adequate removal of fluid and food collected in the subphrenic area and pelvis is often neglected. A thorough examination of the abdomen for possible collections of fluid should be made, with particular reference to the subphenic area, right lumbar gutter, and pelvis, in order to decrease the possibility of abscess formation.

Recently, Taylor [4] has advocated medical management of acute free perforations. We do not believe that this is the policy of choice. Many factors in the abdomen may make it impossible for the body to cope with this emergency. Previous pelvic infection may prevent the omentum from coming up and sealing the perforation. It is impossible to determine the size of the perforation clinically, and large perforations are obviously much harder to wall off. Collections of fluid and gastric contents, though apparently sterile during the early phase of this process in most cases of perforation, are prone to develop into abscesses. Elimination of these collections is a most important part of the treatment and cannot be done by medical means. For these reasons we do not believe that conservative management of a perforation is justified and therefore advocate plication of the ulcer. We are aware that larger doses of antibiotics will enable the body to cope with the infection more adequately, but we maintain that the primary problem remains the closure of the perforated viscus.

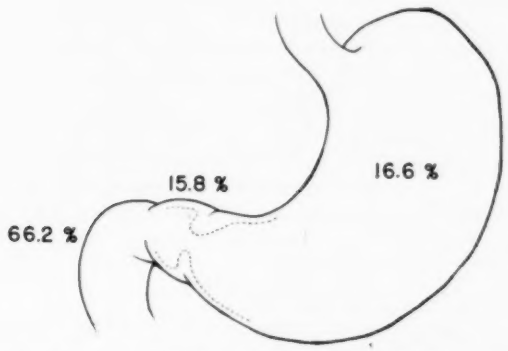
It is difficult to obtain accurate figures on the results of conservative management because of the lack of finality in the diagnosis. Several conditions may mimic acute free perforation, of which some carry an excellent prognosis without surgery. Demonstration of pneumoperitoneum would eliminate doubt in many cases.

Most of the perforations occurred in the anterior duodenum, 66% (Fig. 1) as opposed to only 17% in the stomach, the next commonest site. Perforation at the site of the pylorus comprised 16% of the perforations in the series. Since the majority of peptic ulcers occur in the duodenal area, the higher incidence of perforations there would be expected. Ulcers of the posterior wall can involve continuous structures such as the pancreas. The most frequent emergency complication in this location is bleeding. Multiple ulcers were not a major problem in this series, although in four patients multiple ulcers were seen at autopsy. Only one patient had multiple perforations, a perforated ulcer in the duodenum and another ulcer at the esophageal-gastric junction. Unfortunately, the upper lesion was not recognized at operation and contributed to the death of the patient. Therefore, though multiple free perforations are unusual, they may occur and should be ruled out.

4. Taylor, H.: Perforated Peptic Ulcer Treated Without Operation, Lancet **2**:441-444, 1946.

The mortality rate from perforation is disturbing because it has not decreased in recent years. Even though the procedure used has remained unchanged over the years, it was hoped that the mortality would decrease with the use of antibiotics and with better preoperative preparation and postoperative care. A certain percentage of the patients will be lost from causes unrelated to surgery. For example, a borderline cardiovascular system may collapse with the added strain of acute illness followed by surgery. But meticulous preoperative and postoperative care should minimize cardiovascular hazards. Tragedies from anesthesia accidents have become rare because of the improvements in its administration.

In other patients complications develop that prolong their illness, and they seem to die of the complication rather than of the original perforation. Included in this group would be the patients who die of other ulcer complications, such as bleeding, and not of the perforation itself. Massive hemorrhage superimposed on a postoperative acute perforation creates a truly critical problem. These patients are extremely ill, and the addition of massive hemorrhage greatly enhances the prospect of an



Location of perforations. At operation it is sometimes difficult to determine whether a perforation is in the duodenum or the pylorus. The recorded incidence for this series of 139 perforations, according to the opinion of the surgeons, is as follows: 92 (66.2%) duodenal; 22 (15.8%) pyloric; 23 (16.6%) gastric, and 2 (1.4%) marginal.

unfavorable outcome. Hemorrhaging patients should be treated like any other gastrointestinal bleeders. The initial treatment is conservative, but if there are indications of continued bleeding, gastric resection should be undertaken.

There is also a group of patients who become increasingly toxic after surgery and die despite all therapy. These patients never rally satisfactorily postoperatively, and clinically they appear overwhelmed by the catastrophy.

As was true with the mortality rate, the lack of significant decrease in morbidity from complications during the more recent period was also disappointing. Pulmonary complications, however, decreased from 56.3% in the earlier period to 35.2% in the later years. Aside from this one difference, the morbidity was almost identical for the two periods. Wound infection still occurs despite the use of antibiotics, but it is usually rather superficial, and routine drainage has not been found necessary. Although the use of antibiotics appears adequate, massive dosage is important because it lessens the chance for drug-resistant organisms to develop.

Pulmonary complications still predominate, but the majority result in bronchopneumonia and respond readily to therapy. By and large, the complications are those associated with any major gastric surgery, both as to incidence and type.

The follow-up results of this series were rather interesting and perhaps constitute the most valuable contribution of this study. Of the surviving patients 96.8% were followed, and 69.5% of these, it was found, continued to have or later experienced the severe manifestations or complications of peptic ulcer, namely, bleeding, obstruction, persistent pain, or, more rarely, reperforation. This indicates that perforation is a sign of severe ulcer diathesis and that over two-thirds of the patients with perforation may be expected to have additional difficulty. About one-third of the group could be maintained on conservative treatment, but the regimen had to be strict and the patients very cooperative. We consider our medical treatment to be similar to that employed at other clinics, and we feel that the type of patients we see are not unusual in their financial, emotional, or intellectual status. Yet over two-thirds continue to have trouble from their ulcers despite all medical therapy. For these reasons and because the results from gastric resection continue to be highly encouraging, we are inclined to advocate surgery as soon as these patients begin to have difficulty. In our series, 40.9% of the patients had subsequent definitive surgery. This proportion is likely to increase, for each year additional patients submit to surgery because of the intractable nature of their disease. Indeed, even in this limited follow-up study, with the longest time since perforation being 19 years and the shortest time 1 year, experience shows that the patient who suffers an acute ulcer perforation has only a 30% chance of remaining asymptomatic postoperatively. For this reason, all patients with perforations are told that they are likely to have further ulcer symptoms after plication, and that, failing control by medical measures, definitive surgery will be indicated.

SUMMARY

Experience with 139 consecutive peptic ulcer perforations over a 19-year period is presented. A policy of doing plication only as soon as feasible after hospitalization has been followed. Although the morbidity from complications and the mortality rate have decreased slightly during this period, this decrease has not kept pace with the trend of decreasing risk associated with many surgical procedures. This is true even though the benefits from therapy advancements have been used just as freely for patients with ulcer perforation as for those with other surgical problems. The mortality was high, 16 deaths (11.5%), and the morbidity from postoperative complications as well (30.9%).

Follow-up studies on 96.8% of the patients who recovered from operation show that in 19 years 80 patients, or over two-thirds of this group (69.5%), continued to have, or later experienced, severe manifestations or complications of peptic ulcer. In this series 47 patients (40.9%) had subsequent definitive surgery, usually subtotal gastric resection done at our clinic.

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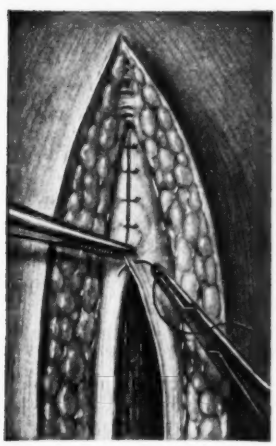

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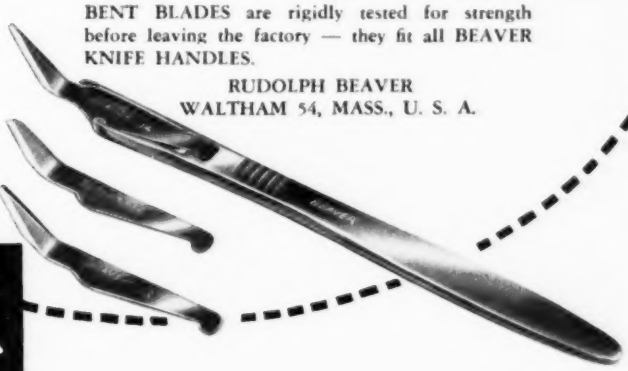

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